1
Structure, Properties, and Preparation of Boronic Acid Derivatives
Overview of Their Reactions and Applications

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1.1
Introduction and Historical Background

Structurally, boronic acids are trivalent boron-containing organic compounds that possess one carbon-based substituent (i.e., a C−B bond) and two hydroxyl groups to fill the remaining valences on the boron atom (Figure 1.1). With only six valence electrons and a consequent deficiency of two electrons, the sp^2-hybridized boron atom possesses a vacant p-orbital. This low-energy orbital is orthogonal to the three substituents, which are oriented in a trigonal planar geometry. Unlike carboxylic acids, their carbon analogues, boronic acids, are not found in nature. These abiotic compounds are derived synthetically from primary sources of boron such as boric acid, which is made by the acidification of borax with carbon dioxide. Borate esters, one of the key precursors of boronic acid derivatives, are made by simple dehydration of boric acid with alcohols. The first preparation and isolation of a boronic acid was reported by Frankland in 1860 [1]. By treating diethylzinc with triethylborate, the highly air-sensitive triethylborane was obtained, and its slow oxidation in ambient air eventually provided ethylboronic acid. Boronic acids are the products of a twofold oxidation of boranes. Their stability to atmospheric oxidation is considerably superior to that of borinic acids, which result from the first oxidation of boranes. The product of a third oxidation of boranes, boric acid, is a very stable and relatively benign compound to humans (Section 1.2.2.3).

Their unique properties and reactivity as mild organic Lewis acids, coupled with their stability and ease of handling, are what make boronic acids a particularly attractive class of synthetic intermediates. Moreover, because of their low toxicity and their ultimate degradation into boric acid, boronic acids can be regarded as "green" (environment-friendly) compounds. They are solids, and tend to exist as mixtures of oligomeric anhydrides, in particular the cyclic six-membered boroxines (Figure 1.1). For this reason and other considerations outlined later in this chapter, the corresponding boronic esters are often preferred as synthetic intermediates. Although other classes of organoboron compounds have found tremendous utility

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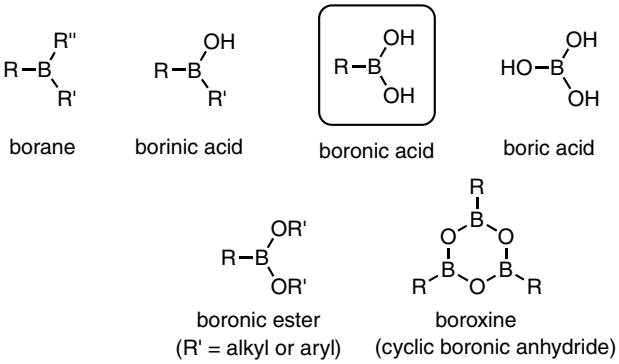


Figure 1.1 Oxygen-containing organoboron compounds.

in organic synthesis, this book focuses on the most recent applications of the convenient boronic acid derivatives. For a comprehensive description of the properties and reactivity of other classes of organoboron compounds, interested readers may refer to a selection of excellent monographs and reviews by Brown [2], Matteson [3], and others [4–8]. In the past two decades, the status of boronic acids in chemistry has gone from that of peculiar and rather neglected compounds to that of a prime class of synthetic intermediates in their own right. The attribution of the 2010 Chemistry Nobel Prize for palladium-catalyzed cross-coupling reactions to Professor Akira Suzuki and other pioneers recognized the great importance of boronic acids in this revolutionary class of C–C bond forming processes. In the past 5 years, impressive advances have been made in the use of boronic acids in molecular recognition, materials science, and catalysis. The approval of the anticancer agent Velcade®, the first boronic acid-containing drug to be commercialized (Section 1.6.5), further confirms the growing status of boronic acids as an important class of compounds in chemistry and medicine. This chapter describes the structural and physicochemical properties of boronic acids and their many derivatives, as well as modern methods for their preparation. A brief overview of their synthetic and biological applications is presented, with an emphasis on topics that are not covered in other chapters of this book.

1.2
Structure and Properties of Boronic Acid Derivatives

1.2.1
General Types and Nomenclature of Boronic Acid Derivatives

The reactivity and properties of boronic acids highly depend upon the nature of their single variable substituent, more specifically, on the type of carbon group (R, Figure 1.1) directly bonded to boron. In the same customary way employed for

other functional groups, it is convenient to classify boronic acids into subtypes such as alkyl-, alkenyl-, alkynyl-, and arylboronic acids.

When treated as an independent substituent, the prefix borono is employed to name the boronyl group (e.g., 3-boronoacrolein). For cyclic derivatives such as boronic esters, the IUPAC RB-1-1 rules for small heterocycles (i.e., the Hantzsch–Widman system) are employed along with the prefix "boro." Thus, saturated five- and six-membered cyclic boronic esters are, respectively, named as dioxaborolanes and dioxaborinanes. For example, the formal name of the pinacol ester of phenylboronic acid is 2-phenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. The corresponding nitrogen analogues are called diazaborolidines and diazaborinanes, and the mixed nitrogen–oxygen heterocycles are denoted by the prefix oxaza. Unsaturated heterocycles wherein the R group and the boron atom are part of the same ring are named as boroles.

1.2.2 Boronic Acids

1.2.2.1 Structure and Bonding

The X-ray crystal structure of phenylboronic acid (**1**, Figure 1.2) was reported in 1977 by Rettig and Trotter [9]. The crystals are orthorhombic, and each asymmetric unit was found to consist of two distinct molecules, bound together through a pair of O−H−O hydrogen bonds (Figure 1.3a and b). The CBO_2 plane is quite coplanar with the benzene ring, with a respective twist around the C−B bond of 6.6° and 21.4° for the two independent molecules of $PhB(OH)_2$. Each dimeric ensemble is also linked with hydrogen bonds to four other similar units to give an infinite array of layers

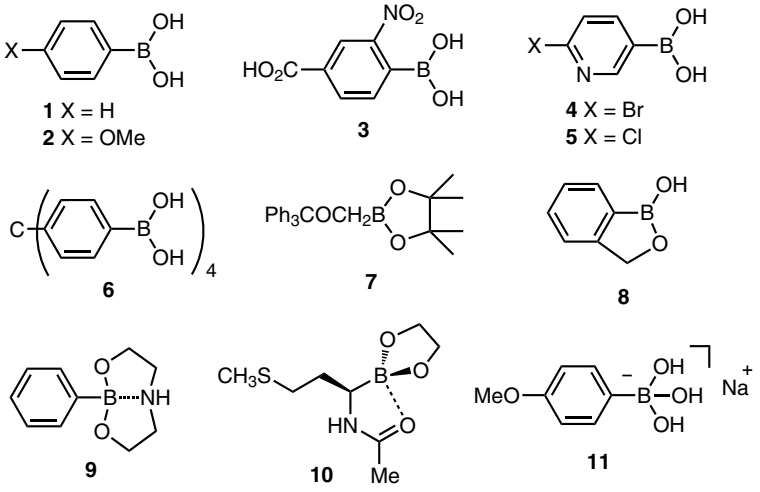


Figure 1.2 Boronic acid derivatives analyzed by X-ray crystallography.

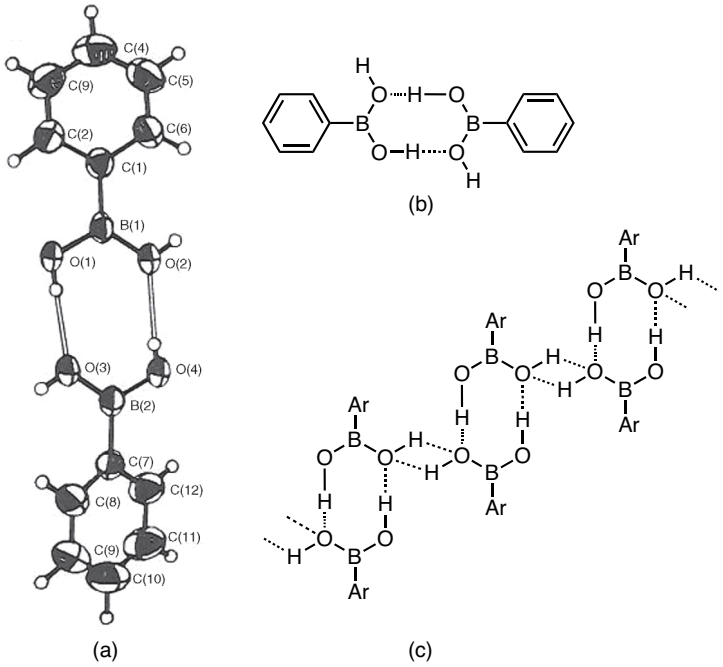


Figure 1.3 Representations of the X-ray crystallographic structure of phenylboronic acid. (a) ORTEP view of a dimeric unit. (b) Structure of the dimeric unit showing hydrogen bonds. (c) Structure of the extended hydrogen-bonded network.

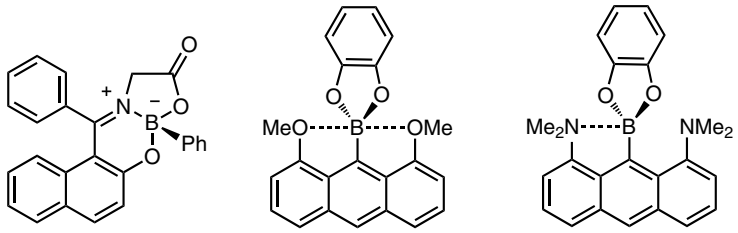
(Figure 1.3c). The X-ray crystallographic analysis of other arylboronic acids like *p*-methoxyphenyl boronic acid (**2**) [10] and 4-carboxy-2-nitrophenylboronic acid (**3**, Figure 1.2) [11] is consistent with this pattern. The structures of heterocyclic boronic acids such as 2-bromo- and 2-chloro 5-pyridylboronic acids (**4** and **5**) were reported [12]. Although the boronate group has a trigonal geometry and is fairly coplanar with the benzene ring in structures **1**, **2**, **4**, and **5**, it is almost perpendicular to the ring in structure **3**. This observation is likely due to a combination of two factors: minimization of steric strain with the *ortho*-nitro group, and because of a possible interaction between one oxygen of the nitro group and the trigonal boron atom. Based on the structural behavior of phenylboronic acid and its propensity to form hydrogen-bonded dimers, diamond-like porous solids were designed and prepared by the crystallization of tetrahedral-shaped tetraboronic acid **6** (Figure 1.2) [13]. With a range of approximately 1.55–1.59 Å, the C−B bond of boronic acids and esters is slightly longer than typical C−C single bonds (Table 1.1). The average C−B bond energy is also slightly smaller than that of C−C bonds (323 versus 358 kJ/mol) [14]. Consistent with strong B−O bonds, the B−O distances of tricoordinate boronic acids such as phenylboronic acid are fairly short, and lie in the range of 1.35–1.38 Å (Table 1.1). These values are slightly larger than those observed in boronic esters. For example, the B−O bond distances observed in the X-ray crystal-

Table 1.1 Bond distances from X-ray crystallographic data for selected boronic acid derivatives (Figure 1.2).

Compound	B–C (Å)	B–O^1 (Å)	B–O^2 (Å)	B–X (Å)	Reference
1	1.568	1.378	1.362		[9]
2	1.556				[10]
3	1.588	1.365	1.346		[11]
4	1.573	1.363	1.357		[12]
5	1.573	1.362	1.352		[12]
7	1.560	1.316	1.314		[15]
8	1.494	1.408	1.372		[16]
9	1.613	1.474	1.460	1.666	[18]
10	1.613	1.438	1.431	1.641	[22]
11	1.631	1.492	1.487	1.471	[23]

lographic structures of the trityloxymethyl pinacolate boronic esters (e.g., **7** in Figure 1.2) are in the range of 1.31–1.35 Å (Table 1.1), and the dioxaborolane unit of these derivatives is nearly planar [15]. The X-ray crystallographic structure of cyclic hemiester **8** (Figure 1.2) was described [16]. Like phenylboronic acid, this benzoxaborole also crystallizes as a hydrogen-bonded dimer, however without the extended network due to the absence of a second hydroxyl group. The cyclic nature of this derivative induces a slight deviation from planarity for the tricoordinate boronate unit, as well as a distortion of the bond angles. The endocyclic B–O bond in **8** is slightly longer than the B–OH bond. This observation was attributed to the geometrical constraints of the ring, which prevents effective lone pair conjugation between the endocyclic oxygen and the vacant orbital of boron. The unique properties and reactivity of benzoxaboroles along with their preparation were recently reviewed [17].

In order to complete boron's octet, boronic acids and their esters may also coordinate basic molecules and exist as stable tetracoordinated adducts. For example, the X-ray crystallographic structure of the diethanolamine adduct of phenylboronic acid (**9**, Figure 1.2) [18] confirmed the transannular B–N bridge long suspected from other spectroscopic evidence such as NMR [19, 20]. This dative B–N bond has a length of 1.67 Å (Table 1.1), and it induces a strong $N^{\delta+}-B^{\delta-}$ dipole that points away from the plane of the aryl ring. This effect was elegantly exploited in the design of a diboronate receptor for paraquat [21]. Chelated boronic ester **10** presents characteristics similar to that of **9** [22]. Trihydroxyborate salts of boronic acids are discrete, isolable derivatives that had not been characterized until recently [23]. The sodium salt of *p*-methoxyphenyl boronic acid (**11**) was recrystallized in water and its X-ray structural elucidation showed the borate unit in the expected hydrogen bonding network accompanied with the sodium cation coordinated with six molecules of water. In principle, the boron atom in tetrahedral complexes can be stereogenic if it is bonded to four different ligands. Hutton and coworkers recently reported the first example of one such optically pure complex stereogenic at boron only [24]. Stable complex **12** (Figure 1.4) was made through a chirality transfer process described in



12 **13** **14**

Figure 1.4 *B*-Chiral tetrahedral boronate **12** and model compounds for boron hypercoordination.

Section 1.2.3.6. When tetracoordinated such as in structures **9–11** [23] (Figure 1.2), the B−O bond length of boronic acids and esters increases to about 1.43–1.48 Å, which is as much as 0.10 Å longer than the corresponding tricoordinate analogues (Table 1.1). These markedly longer B−O bonds are comparable to normal C−O ether bonds (∼1.43 Å). These comparisons further emphasize the considerable strength of B−O bonds in trigonal boronic acid derivatives. Not surprisingly, trigonal B−O bonds are much stronger than the average C−O bonds of ethers (519 versus 384 kJ/mol) [14]. This bond strength is believed to originate from the conjugation between the lone pairs on the oxygens and boron's vacant orbital, which confers partial double bond character to the B−O linkage. In fact, it was estimated that formation of tetrahedral adducts (e.g., with NH_3) may result in a loss of as much as 50 kJ/mol of B−O bond energy compared to the tricoordinate boronate [25].

In rare instances where geometrical factors allow it, boronic acid derivatives may become hypervalent. For example, the catechol ester **13** (Figure 1.4) was found by X-ray crystallographic analysis to be pentacoordinated in a highly symmetrical fashion as a result of the rigidly held ether groups, which are perfectly positioned to each donate lone pair electrons to both lobes of the vacant p-orbital of boron [26]. The boronyl group of this two electron–three atom center is planar, in a sp^2 hybridization state, and the resulting structure possesses a slightly distorted trigonal bipyramidal geometry. According to DFT calculations, the bonding is weak and ionic in nature [26b]. The corresponding diamine **14**, however, behaved quite differently and demonstrated coordination with only one of the two NMe_2 groups [27].

Due to electronegativity differences (B = 2.05, C = 2.55) and notwithstanding the electronic deficiency of boron, which is compensated by the two electron-donating oxygen atoms (see above), the inductive effect of a boronate group should be that of a weak electron donor. The ^{13}C NMR alpha effect of a boronate group is in fact very small [28]. On the other hand, the deficient valency of boron and its size relatively similar to that of carbon have long raised the intriguing question of possible pi-bonding between carbon and boron in aryl- and alkenylboronic acids and esters [29]. NMR data and other evidence, such as UV and photoelectron spectroscopy and LCAO-MO calculations, suggest that B−C pi-conjugation occurs to a moderate extent in alkenylboranes [30–32], and is even smaller in the case of the considerably less acidic boronate derivatives. A thorough comparative study of ^{13}C NMR shift effects,

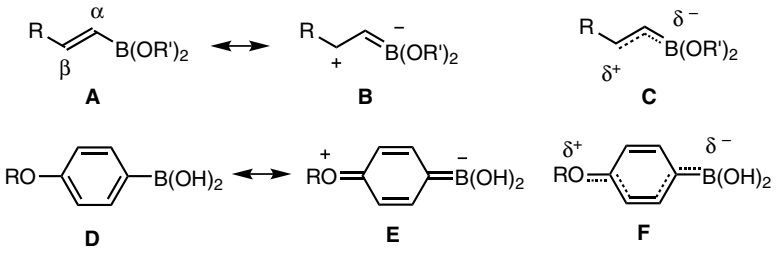


Figure 1.5 Limit mesomeric forms involving B−C pi-overlap.

in particular the deshielding of the beta-carbon, concluded to a certain degree of mesomeric pi-bonding in the case of boranes and catechol boronates [28]. For example, compared to analogous aliphatic boronates, the beta-carbons of a dialkyl alkenylboronate and the corresponding catechol ester are deshielded by 8.6 and 18.1 ppm, respectively. In all cases, the beta-carbon is more affected by the boronate substituent than the alpha-carbon, which is consistent with some contribution from the B−C pi-bonded form **B** to give resonance hybrid **C** (Figure 1.5). X-ray crystallography may also provide insights into the extent of B−C pi-bonding. The difference in B−C bond distances for arylboronic acids (Table 1.1) is significant enough to suggest a small degree of B−C pi-bonding. The B−C bond distance (1.588 Å) in the electron-poor boronic acid **3**, which is incapable of pi-conjugation because it has its vacant p-orbital placed orthogonally to the pi-system of the phenyl ring, is expectedly longer than that of phenylboronic acid (1.568 Å). Interestingly, the B−C bond of **2** stands at 1.556 Å, suggesting only a minimal contribution from the mesomeric form **E** (Figure 1.5). On the other hand, the B−C bond distance of 1.613 Å in the diethanolamine adduct **9** (Table 1.1), where the boron vacant orbital is also incapacitated from B−C pi-bonding, is 0.045 Å longer than that of free phenylboronic acid (**1**). In so far as bond length data correlate with the degree of pi-bonding [33], this comparison is consistent with a small B−C pi-bonding effect in arylboronic acids and esters (i.e., hybrid form **F** in Figure 1.5). This view is further supported by chemical properties such as substituent effects on the acidity of arylboronic acids (see Section 1.3.8.3) and ^{11}B chemical shifts correlations [34]. Likewise, B−C pi-bonding is also present in alkenylboronic acids and esters, but this effect must be weak in comparison to the electron-withdrawing effect of a carbonyl or a carboxyl group. For instance, alkenylboronic esters do not readily act as Michael acceptors with organometallic reagents in the same way as the unsaturated carbonyl compounds do [35]. On the other hand, the formal electron-withdrawing behavior of the boronate group manifests itself in cycloadditions of dibutylethylene boronate with ethyldiazoacetate [36] and in Diels–Alder reactions where it provides cycloadducts with dienes like cyclopentadiene [37] and cyclohexadiene, albeit only at elevated temperatures (about 130 and 200 °C, respectively) [38, 39]. The higher reactivity of ethylene boronates as dienophiles compared to ethylene has been rationalized by MO calculations [29], but their reactivity stands far from that of acrylates in the same cycloadditions. In fact, more recent high-level calculations suggest that the reactivity of alkenylboronates

may be mainly due to a three-atom–two-electron center stabilization of the transition state rather than a true LUMO-lowering electron-withdrawing mesomeric effect from the boronate substituent [40]. Another evidence for the rather weak electron-withdrawing character of boronic esters comes from their modest stabilizing effect on boronyl-substituted carbanions, where their effect has been compared to that of a phenyl group (see Section 1.3.8.3).

1.2.2.2 Physical Properties and Handling

Most boronic acids exist as white crystalline solids that can be handled in air without special precautions. At the ambient temperature, boronic acids are chemically stable and most display shelf stability for long periods of time (Section 1.2.2.5). Alkyl-substituted and some heteroaromatic boronic acids, however, were shown to have a limited shelf stability under aerobic conditions [41]. Boronic acids normally do not tend to disproportionate into their corresponding borinic acid and boric acid even at high temperatures. To minimize atmospheric oxidation and autoxidation, however, they should be stored under an inert atmosphere. When dehydrated, either with a water-trapping agent or through coevaporation or high vacuum, boronic acids form cyclic and linear oligomeric anhydrides such as the trimeric boroxines already mentioned (Figure 1.1). Fortunately, this behavior is usually inconsequential when boronic acids are employed as synthetic intermediates. Many of their most useful reactions (Section 1.5), including the Suzuki-Miyaura cross-coupling, proceed regardless of the hydrated state (i.e., free boronic acid or anhydride). Anhydride formation, however, may complicate analysis, quantitation, and characterization efforts (Section 1.4.3). Furthermore, upon exposure to air, dry samples of boronic acids may be prone to decompose rapidly, and it has been proposed that boronic anhydrides may be initiators of the autoxidation process [42]. For this reason, it is often better to store boronic acids in a slightly moist state. Presumably, coordination of water or hydroxide ions to boron protects boronic acids from the action of oxygen [42, 43]. Incidentally, commercial samples tend to contain a small percentage of water that may help in their long-term preservation. Due to their facile dehydration, boronic acids tend to provide somewhat unreliable values of melting points (Section 1.4.3.1). This inconvenience and the other above-mentioned problems associated with anhydride formation explain in large part the popularity of boronic esters and other derivatives as surrogates of boronic acids (Section 1.2.3.2).

The Lewis acidity of boron in boronic acids and the hydrogen bond donor capability of their hydroxyl groups combine to lend a polar character to most of these compounds. Although the polarity of the boronic acid head can be mitigated by a relatively hydrophobic tail as the boron substituent, most small boronic acids are amphiphilic. Phenylboronic acid, for instance, was found to have a benzene–water partition ratio of 6 [44]. The partial solubility of boronic acids in both neutral water and polar organic solvents often complicates isolation and purification efforts (Section 1.4). Evidently, boronic acids are more water soluble in their ionized form in high-pH aqueous solutions and can be extracted more readily into organic solvents from aqueous solutions of low pH (see Section 1.2.2.4).

1.2.2.3 **Safety Considerations**

As evidenced by their application in medicine (Chapter 13), most boronic acids present no particular toxicity compared to other organic compounds [45]. Small water-soluble boronic acids demonstrate low toxicity levels, and are excreted largely unchanged by the kidney [46]. Larger fat-soluble boronic acids were found to be moderately toxic [46–48]. At high doses, boronic acids may interact promiscuously with nucleophilic enzymes and complex weakly to biological diols (Section 1.2.3.2.3). Boronic acids present no particular environmental threat, and the ultimate fate of all boronic acids in air and aqueous media is their slow oxidation into boric acid. The latter is a relatively innocuous compound, and may be toxic only under high daily doses [49]. A single acute ingestion of boric acid does not even pose a threatening poisoning effect to humans [50] unless it is accompanied by other health malfunctions such as dehydration [51].

1.2.2.4 **Acidic Character**

By virtue of their deficient valence, boronic acids possess a vacant p-orbital. This characteristic confers them unique properties as a mild class of organic Lewis acids capable of coordinating basic molecules. When doing so, the resulting tetrahedral adducts acquire a carbon-like configuration. Thus, despite the presence of two hydroxyl groups, the acidic character of most boronic acids is not that of a Brønsted acid (i.e., oxyacid) (Equation 1.1, Figure 1.6) but usually that of a Lewis acid (Equation 1.2). When coordinated with an anionic ligand, the resulting negative charge is formally drawn on the boron atom, but it is in fact spread out on the three heteroatoms.

1.2.2.4.1 **Complexation Equilibrium in Water and Structure of the Boronate Anion**

Boronic acids are more soluble in aqueous solutions of high pH (>8). Although the acidic character of boronic acids in water had been known for several decades, it is only in 1959 that the structure of the boronate ion, the conjugate base, was elucidated. In their classical paper on polyol complexes of boronic acids [52], Lorand and Edwards demonstrated that the trivalent neutral form, likely hydrated, is in equilibrium with the anionic tetrahedral species (Equation 1.2, Figure 1.6) and not with the structurally related Brønsted base (i.e., the trivalent ion shown in Equation 1.1). The first X-ray crystallographic structure of a trihydroxyboronate salt has been reported recently (**11** in Figure 1.2) [23]. It is this ability to ionize water and form hydronium ions by "indirect" proton transfer that characterizes the acidity of most boronic acids in water. Hence, the most acidic boronic acids possess the most

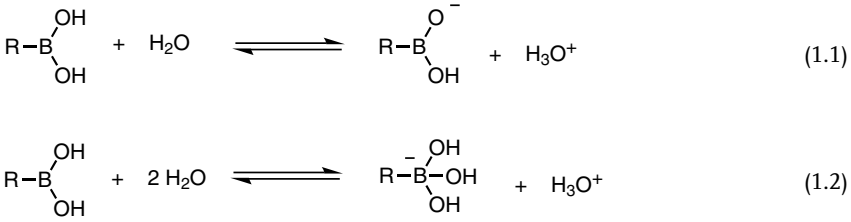
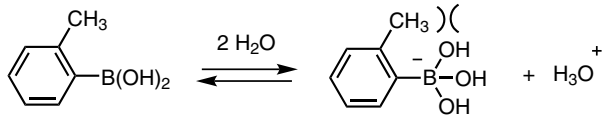


Figure 1.6 Ionization equilibrium of boronic acids in water.

Table 1.2 Ionization constant (pK_a) for selected boronic acids.

Boronic acid, $RB(OH)_2$	pK_a	Reference
Boric acid, $B(OH)_3$	9.0	[58]
Methyl	10.4	[58]
Phenyl	8.9	[59]
3,5-Dichlorophenyl	7.4	[59]
3,5-Bis(trifluoromethyl)phenyl	7.2	[59]
2-Methoxyphenyl	9.0	[57]
3-Methoxyphenyl	8.7	[59]
4-Methoxyphenyl	9.3	[60]
4-Carboxyphenyl	8.4	[56]
2-Nitrophenyl	9.2	[61]
4-Nitrophenyl	7.1	[60]
4-Bromophenyl	8.6	[59]
4-Fluorophenyl	9.1	[59]
2-Methylphenyl	9.7	[62]
3-Methylphenyl	9.0	[62]
4-Methylphenyl	9.3	[62]
3,5-Dimethylphenyl	9.1	[59]
3-Methoxycarbonyl-5-nitrophenyl	6.9	[63]
2-Fluoro-5-nitrophenyl	6.0	[57]
3-Pyridyl (**15**)	4.0, 8.2	[64]
3-Benzyl-3-pyridylium	4.2	[57]
8-Quinolinyl	4.0, 10	[65]
2-($R^1R^2NCH_2$)phenyl (e.g., **16**)	5.2–5.8	[66]

electrophilic boron atom that can best form and stabilize a hydroxyboronate anion. The acidity of boronic acids in water has been measured using electrochemical methods as early as the 1930s [53–55]. Values of pK_a are now measured more conveniently by UV spectrophotometry [56] and ^{11}B NMR spectroscopy. Phenylboronic acid, with a pK_a value of 8.9 in water, has an acidity comparable to a phenol (Table 1.2). It is slightly more acidic than boric acid (pK_a 9.2). With the pK_a values as shown in Table 1.2, the relative order of acidity for the different types of boronic acids is aryl > alkyl. More values can be found elsewhere [57]. For *para*-monosubstituted aromatic boronic acids, the relationship between the pK_a and the electronic nature of the substituent can be described with a Hammet plot [57]. Bulky substituents proximal to the boronyl group can decrease the acid strength due to steric inhibition in the formation of the tetrahedral boronate ion. For example, *ortho*-tolylboronic acid is slightly less acidic than its *para*-isomer (pK_a 9.7 versus 9.3, Table 1.2) [62]. This difference was explained in terms of F-strain in the resulting ion (Equation 1.3, Figure 1.7) [67]. As expected, the presence of electron-withdrawing substituents in the aryl group of arylboronic acids increases the acid strength by a fairly significant measure [53, 55, 60, 68]. For example, the highly electron-poor 3-methoxycarbonyl-5-nitrophenyl boronic acid was attributed a pK_a value of 6.9 [63]. Exceptionally, *ortho*-nitrobenzeneboronic acid [61] is much less acidic than its *para*-isomer [60] (pK_a 9.2 versus 7.1, Table 1.2) presumably due to internal coordination of



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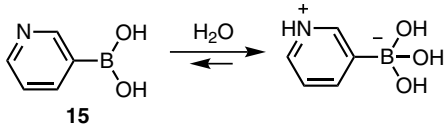

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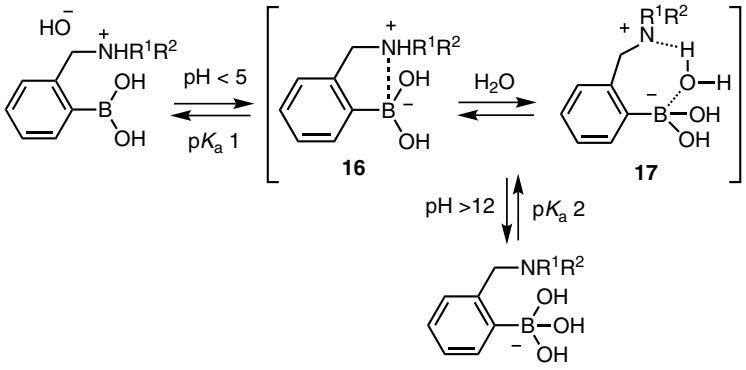

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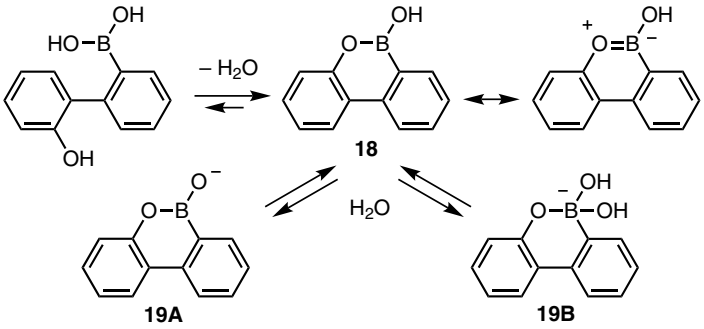

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Figure 1.7 Ionization equilibrium of special boronic acids.

one of the nitro oxygens that prevents the complexation of a hydroxyl anion [55]. Perhaps one of the most acidic of all known boronic acids, with a pK_a of approximately 4.0, 3-pyridylboronic acid (**15**) exists mainly as a zwitterion in water (Equation 1.4, Figure 1.7) [64]. Similarly, arylboronic acids of type **16** (Equation 1.5), which benefit from anchimeric participation of the *ortho*-dialkylaminomethyl group, display a relatively low value of pK_a of about 5.2 [66]. In this case, the actual first pK_a is that of ammonium ion deprotonation and formation of the putative tetrahedral B−N ate adduct **16**. The latter form was shown to exist in organic solvents, but in water and other hydroxylic solvents, complex **17** forms through a water-insertion mechanism [69]. The application of boronic acids of type **16** in the aqueous recognition

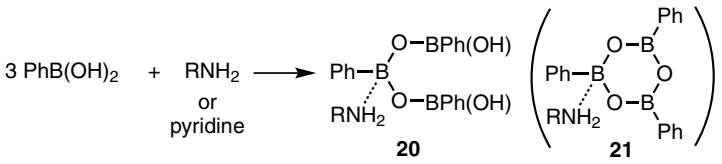
of saccharides is briefly discussed in Chapter 13. Fluoride ions also form strong dative bonds with boron, and it has been noted long ago that boronic acids dissolved in aqueous solutions of hydrofluoric acid are very difficult to extract into organic solvents unless the fluoride is precipitated out [70].

Boronic acids display Brønsted acidity (cf. Equation 1.1, Figure 1.6) only in exceptional cases where the formation of a tetrahedral boronate adduct is highly unfavorable. For example, coordination of hydroxide ion to boron in heterocyclic boronic acid derivative **18**, to form **19B**, would break the partial aromatic character of the central ring (Equation 1.6, Figure 1.7). Indeed, based on ^{11}B NMR and UV spectroscopic evidence, it was suggested that **18** acts as a Brønsted acid in water and forms conjugate base **19A** through direct proton transfer [71]. A small number of other boronic acids are suspected of behaving as Brønsted acids due to the same reasons [72].

1.2.2.4.2 **Bimolecular Lewis Acid–Base Complexation under Nonaqueous Conditions** As evidenced by the high pH required in the formation of boronate anions, boronic acids and most dialkyl esters are weak Lewis acids. This behavior is in sharp contrast with trialkylboranes, which form strong adducts with phosphines, amines, and other Lewis bases [73]. Apart from the formation of boronate anions, discussed in the previous section, very few examples of stable intermolecular acid–base adducts of boronic acids (esters) exist. It has been known for a long time that aliphatic amines and pyridine can form complexes in a 1 : 3 amine:boronic acid stoichiometry [74]. Combustion analyses of these air-stable solids suggested that two molecules of water are lost in the process, which led the authors to propose structure **20** (Equation 1.7, Figure 1.8). Much later, Snyder *et al*. used IR spectroscopy to demonstrate that these 1 : 3 complexes rather involved the fully dehydrated boroxine (**21**) [75]. Boronic esters are generally weak Lewis acids but catechol boronates are quite acidic, and provided that cooperative effects are exploited, bimolecular complexes with fluoride anions and amines have been reported [76–78]. The B−F bond strength is a key factor in these complexes as other halide salts do not form similar adducts. As suggested by ^{1}H NMR spectroscopic studies, an *ortho*-phenyldiboronic ester (**22**) showed cooperative binding of two amine molecules in putative complex **24** (Equation 1.8, Figure 1.8) [79]. Other diboronate receptors were found to bind to diamines selectively using the two boron centers for B−N coordination [80–82]. Catechol esters and other cyclic five-membered boronic esters with sp^2 centers are more acidic as complexation to form a tetrahedral boron atom relieves strain. The concept of strain has recently been exploited in the design of a receptor with photoswitchable Lewis acidity [83]. Pyridine complexation studies by ^{1}H NMR spectroscopy showed that bisthiophene boronate receptor **25** is more acidic in its closed cross-conjugated form **26** compared to the less strained, open form **25** (Equation 1.9).

1.2.2.5 Chemical Stability

1.2.2.5.1 **Ligand Exchange and Disproportionation** Several favorable factors contribute to the stability of boronic acids and their esters. Substitution of the carbon-containing group of boronic acids with other substituents is a slow process, and B−C/B−O bond metatheses to give the corresponding disproportionation products



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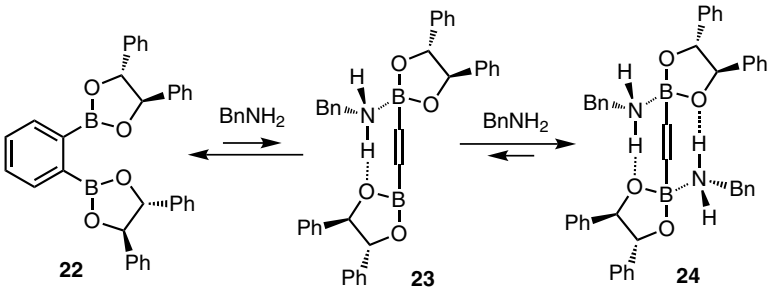

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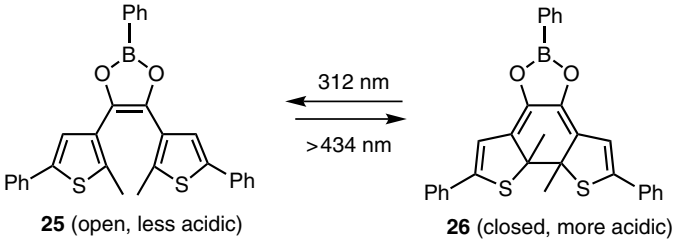


(1.9)

Figure 1.8 Bimolecular Lewis acid–base complexes with boronic esters.

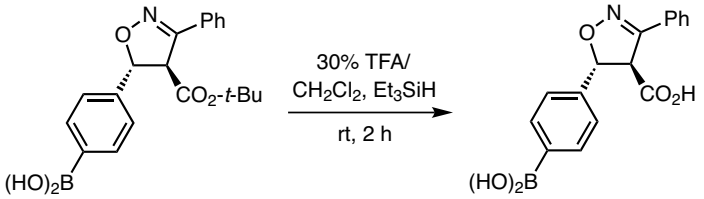
(trialkylborane, borinic acid, or boric acid) are thermodynamically unfavorable [25]. This redox disproportionation is rather used to transform borinic esters into boronic esters [84]. Similarly, thermodynamic considerations make the exchange of the hydroxyl substituents of boronic acids with other ligands quite unfavorable. Substitution with most alcohols or diols to form boronic esters usually requires dehydration techniques in order to drive the reaction forward (Section 1.2.3.2.1). In general, from the B–X bond energy values of all possible boronic acid derivatives (RBX_2), it can be said that free boronic acids remain unchanged when dissolved in solutions containing other potential anionic ligands [24]. The only type of B–X bond stronger than a B–O bond is the B–F bond. Chemical methods to accomplish this type of exchange and other B–O bond derivatizations are described in Sections 1.2.3.7 and 1.2.3.8.

1.2.2.5.2 **Atmospheric Oxidation** A significant thermodynamic drive for C–B bond oxidation results as a direct consequence of the large difference between B–O and B–C bond energies (Section 1.2.2.1). Heats of reaction for the oxidative cleavage of methylboronic acid with water and hydrogen peroxide are −112 and −345 kJ/mol, respectively [25]. Yet, fortunately for synthetic chemists, oxidative cleavage of the B–C bond of boronic acid derivatives with water or oxygen is a kinetically slow process, and most boronic acids can be manipulated in ambient air and are stable in water in a wide

range of pH. This is particularly true for aryl- and alkenylboronic acids, and in general, samples of all types of boronic acids tend to be significantly more stable when moist (coordination of water to boron likely acts as a protection) (Section 1.2.2.2) [42, 43, 85]. Exceptionally, the highly electron-poor arylboronic acid 4-carboxy-2-nitrophenylboronic acid was reported to undergo slow oxidation to the corresponding phenol when left in aqueous basic solutions (pH 9) [11]. On the other hand, basic aqueous solutions of alkylboronate ions were claimed to be highly tolerant of air oxidation [42]. Free alkylboronic acids, however, are quite prone to a slow atmospheric oxidation and variable amounts of the corresponding alcohols may form readily when dried samples are left under ambient air. Likewise, solutions of arylboronic acids in tetrahydrofuran devoid of stabilizer may turn rapidly into the corresponding phenols. The propensity of alkylboronic acids to undergo autoxidation depends on the degree of substitution, with primary alkyl substituents being less reactive than the secondary and tertiary alkyl substituents, respectively [85]. More potent oxidants such as peroxides readily oxidize all types of boronic acids and their corresponding esters (Section 1.5.2.1). This propensity for oxidation must be kept in mind while handling boronic acids.

1.2.2.5.3 **Protolytic Deboronation** Most types of boronic acids are highly resistant to protolysis of the C—B bond in neutral aqueous solutions even at high temperatures. For example, *p*-tolylboronic acid was recovered unchanged after 28 h in boiling water [86]. Aqueous protodeboronation can become problematic at higher temperatures; *p*-tolylboronic acid was completely deboronated to toluene after 6 h under pressure at 130–150 °C [86]. Deboronation of arylboronic acids can be effected quite readily in highly acidic or basic aqueous solutions [87]. In particular, *ortho*-substituted and especially electron-poor arylboronic acids are notorious for their propensity to protodeboronate under basic aqueous conditions, a process that can be exacerbated by exposure to light [64]. Consequently, competitive deboronation may plague some reactions employing boronic acids as reagents like the Suzuki–Miyaura cross-coupling reaction (Section 1.5.3.1), which requires basic conditions often at high temperatures. Under acidic aqueous conditions, however, the more electron-rich arylboronic acids tend to deboronate faster [87, 88]. For example, *p*-carboxyphenylboronic acid was found to be more tolerant than phenylboronic acid to the highly acidic conditions of ring nitration under fuming nitric acid and concentrated sulfuric acid [89]. Certain heteroaromatic boronic acids with the boronyl group next to the heteroatom (α-substituted) are notoriously prone to protodeboronation, but they can be stabilized as tetrahedral adducts (Section 1.2.3.3) [41, 90]. The effect of acid, temperature, and ring substitution of arylboronic acids on the kinetics of electrophilic protolytic deboronation with strong aqueous acid has been studied by Kuivila and Nahabedian [91]. A relatively complex behavior was found, and at least two possible pH-dependent mechanisms were proposed. In contrast to their behavior with aqueous acids, most arylboronic acids and esters appear to be very resistant to nonaqueous acids, as evidenced by their recovery from reaction processes using strong organic acids. For example, a phenolic methoxymethyl ether was deprotected with a 2 : 1 CH_2Cl_2/CF_3CO_2H (TFA) mixture that left intact a pinacol boronic ester functionality [92]. Likewise, free arylboronic acids have been shown to tolerate, at ambient temperature, similar organic acid conditions that effect cleavage of *t*-butoxycarbonyl groups (Equation 1.10) [93]. On the other hand,

a report emphasized that arylboronic acids can be protodeboronated thermally without added acid by prolonged heating in refluxing ethereal solvents [94].



(1.10)

In contrast to arylboronic acids, early reports document the great stability of alkylboronic acids under aqueous acidic solutions. For example, a variety of simple alkylboronic acids were unaffected by prolonged heating in 40% aqueous HBr or HI [42]. Like arylboronic acids, however, deboronation is observed in hot basic aqueous solutions [85]. Alkenylboronic esters undergo protonolysis in refluxing AcOH [95], and alkynylboronic acids were reported to be quite unstable in basic aqueous solutions (Section 1.3.5).

All types of boronic acids can be protodeboronated by means of metal-promoted C–B bond cleavage, and these methods are described separately later in this chapter (Section 1.5.1).

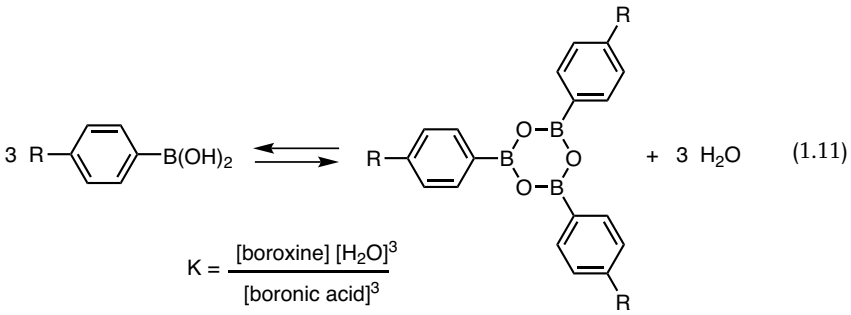
1.2.3 Boronic Acid Derivatives

For the sake of convenience in their purification and characterization, boronic acids are often best handled as ester derivatives where the two hydroxyl groups are masked. On the other hand, transformation of the hydroxyl groups into other substituents such as halides or borate salts may also provide an increase in reactivity necessary for a number of synthetic applications. The next sections describe the most important classes of boronic acid derivatives.

1.2.3.1 Boroxines (Cyclic Anhydrides)

Boroxines are the cyclotrimeric anhydrides of boronic acids. Their properties and applications have been reviewed recently [96]. By virtue of boron's vacant orbital, boroxines are isoelectronic to benzene, but it is generally accepted that they possess little aromatic character [97]. Several theoretical and experimental studies have addressed the nature and structure of these derivatives [96]; in particular, the X-ray crystallographic analysis of triphenylboroxine confirmed that it is virtually flat [98]. Boroxines are easily produced by the simple dehydration of boronic acids, either thermally through azeotropic removal of water or by exhaustive drying over sulfuric acid or phosphorus pentoxide [42]. These compounds can be employed invariably as substrates in many of the same synthetic transformations known to affect boronic acids. Interest in the applications of boroxines as end products has increased in the past decade. Their use has been proposed as flame retardants [99] and as functional materials (see Chapter 14) [100]. The formation of boroxine cross-linkages has been employed as a means to immobilize blue light-emitting oligofluorene diboronic

acids [101]. Samples of boroxines, which may also contain oligomeric acyclic analogues, were found to be sensitive to autoxidation when dried exhaustively (Sections 1.2.2.2 and 1.2.2.5.2). A study examined the thermodynamic parameters of boroxine formation in water (Equation 1.11) [102]. Using ^{1}H NMR spectroscopy, the reaction was found to be reversible at room temperature, and the equilibrium constants, relatively small ones, were found to be subject to substituent effects. For example, boroxines with a *para*-electron-withdrawing group have smaller equilibrium constants. This observation was interpreted as an outcome of a back-reaction (i.e., boroxine hydrolysis) that is facilitated by the increased electrophilicity of boron. Steric effects also come into play, as indicated by a smaller *K*-value for *ortho*-tolylboronic acid compared to the *para*-isomer. Variable temperature studies provided useful thermodynamic information, which was found consistent with a significant entropic drive for boroxine formation due to the release of three molecules of water.



1.2.3.2 **Boronic Esters**

By analogy with carboxylic acids, the replacement of the hydroxyl groups of boronic acids by alkoxy or aryloxy groups provides esters. By losing the hydrogen bond donor capability of the hydroxyl groups, boronic esters are less polar and easier to handle. They also serve as protecting groups that can mitigate the particular reactivity of boron–carbon bonds. Most boronic esters with a low molecular weight are liquid at room temperature and can be conveniently purified by distillation. Exceptionally, the trityloxymethyl esters described above are crystalline solids [15]. A selection of the most commonly encountered boronic esters is shown in Figure 1.9. Many of these esters are chiral and have also been used as inducers in stereoselective reactions discussed in Section 1.3.8.4. In addition, a number of macrocyclic oligomeric esters have been described [103].

1.2.3.2.1 **Stoichiometric Formation in Nonaqueous Conditions** The preparation of boronic esters from boronic acids and alcohols or diols is straightforward (Equation 1.12, Figure 1.9). The overall process is an equilibrium and the forward reaction is fast with preorganized diols, and particularly favorable when the boronate product is insoluble in the reaction solvent. The backward process (hydrolysis) can be slowed to a practical extent by using bulky diols such as pinanediol or pinacol. Otherwise, ester formation can be driven by azeotropic distillation of the water produced using a Dean–Stark apparatus or, alternatively, with the use of a dehydrating agent (e.g.,

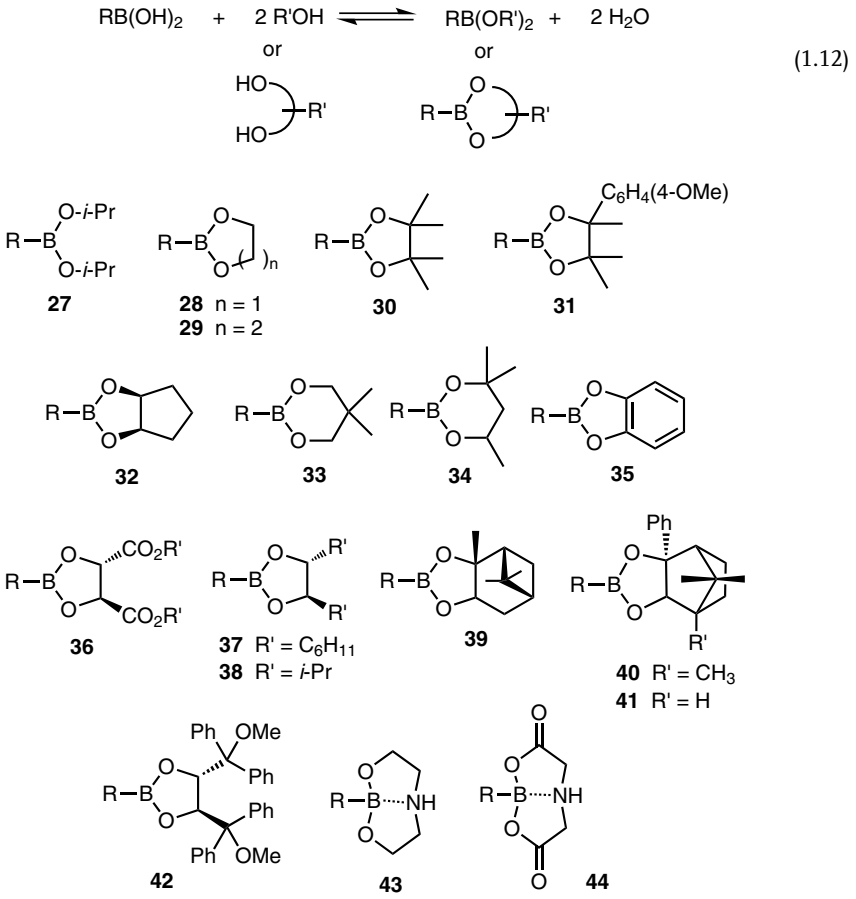
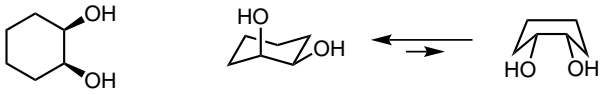


Figure 1.9 Common types of boronic esters.

$MgSO_4$, molecular sieves, etc.). The use of mechanochemistry (i.e., solvent-less grinding) has been reported for the preparation of cyclic esters by condensation of certain diols with aliphatic and aromatic boronic acids [104]. Boronic esters can also be made by transesterification of smaller dialkyl esters like the diisopropyl boronates, with distillation of the volatile alcohol by-product driving the exchange process. In the case of cyclic esters made from the more air-sensitive alkylboronic acids, an alternate method involves treatment of a diol with lithium trialkylborohydrides [105]. Likewise, cyclic ethylboronates were prepared by reaction of polyols with triethylborane at elevated temperatures [106]. One of the first reports on the formation of boronic esters from diols and polyols, by Kuivila *et al.*, described the preparation of several esters of phenylboronic acid by reaction of the latter, in warm water, with sugars like mannitol and sorbitol and 1,2-diols like catechol and pinacol [107]. The desired nonpolar boronic esters precipitated upon cooling the solution. Interestingly, *cis*-1,2-cyclohexanediol failed to provide the corresponding cyclic ester and the authors rationalized this observation on the basis of the unfavorable diol geometry of



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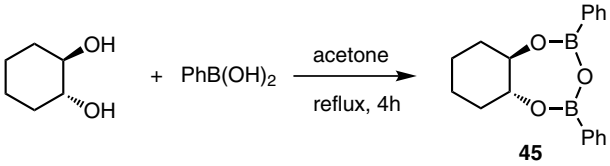

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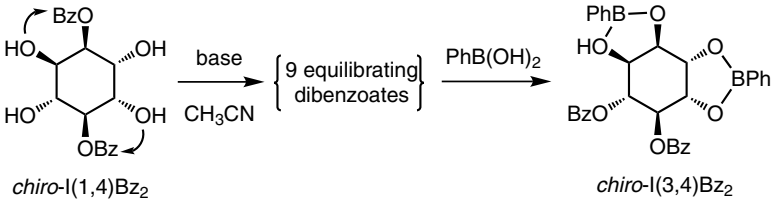


(1.15)

Figure 1.10 Specific examples of boronic ester formation with cyclic diols.

the substrate. Thus, although the two diols are not oriented in the same plane in the chair conformation (Equation 1.13, Figure 1.10), they can adopt such a favorable orientation only in the boat conformer, which is thermodynamically unfavorable [107]. Under anhydrous conditions (i.e., refluxing acetone), phenylboronic esters of *cis*-1,2-cyclopentanol and *cis*-1,2-cyclohexanol can be isolated [108]. The *trans*-isomers, however, failed to give a 1 : 1 adduct, and based on elemental analysis and molecular weight determinations, rather gave 1 : 2 adducts such as **45** (Equation 1.14). The existence of a seven-membered *trans* 1 : 2 adduct of a glucopyranoside was recently demonstrated by NMR spectroscopy [109]. This behavior can be explained in terms of the large energy required for the *trans*-diol to adopt a coplanar orientation, which would increase ring strain and steric interactions between axial atoms. The marked preference for the formation of boronic esters from cyclic *cis*-diols was exploited in the concept of dynamical combinatorial chemistry, using phenylboronic acid as a selector to amplify and accumulate one out of nine possible dibenzoate isomers of chiro-inositol that exist under equilibrating conditions through base-promoted intramolecular acyl migration (Equation 1.15) [110]. The relative thermodynamic stability of several boronic esters was examined by comparing the equilibrium composition of products in the transesterification of 2-phenyl-1,3,2-dioxaborolane with various diols by NMR spectroscopy in deuterated chloroform (Figure 1.11) [111]. Rigid, preorganized diols like pinanediol (**39**) provide the most robust esters and it was also found that six-membered esters are generally more stable than the corresponding five-membered boronates (i.e., **29** versus **28**). Presumably, the stabilizing effect of B–O conjugation via overlap of boron with oxygen lone pairs is geometrically optimal in the larger rings. Diethanolamine boronic esters (**43**, Figure 1.9) represent a useful class of boronic acid derivatives [112].

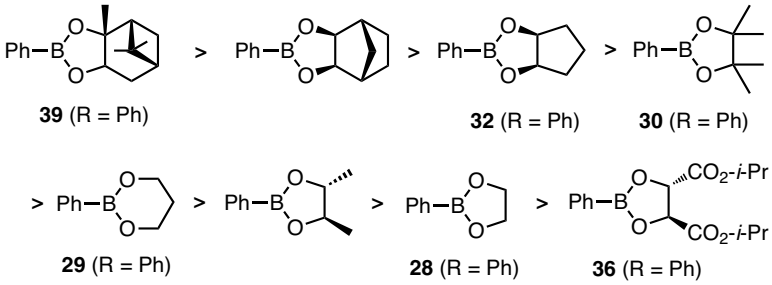


Figure 1.11 Relative thermodynamic stability in a series of boronic esters.

Other *N*-substituted derivatives were characterized [113]. The presence of internal coordination between the nitrogen lone pair and boron's vacant orbital constitutes a unique structural characteristic of these tetrahedral derivatives. This coordination makes the hydrolysis reaction less favorable and even stabilizes the boron atom against atmospheric oxidation. Diethanolamine boronic esters can be conveniently formed in high yields, often without any need for dehydration techniques, as they tend to crystallize out of solution. These adducts are solids, often crystalline, with sharp melting points, and can thus be used for purifying and characterizing boronic acids, as well as in the chemical protection of the boronyl group toward various transformations (see Section 1.3.8.6). The concept of internal coordination in diethanolamine esters has been exploited in the development of the DEAM-PS resin for immobilization and derivatization of boronic acids (Section 1.4.2.1).

1.2.3.2.2 **Hydrolysis and Cleavage** From a thermodynamic standpoint, the stability of B–O bonds in boronic acids and their ester derivatives is comparable (Section 1.2.2.1). Consequently, hydrolysis, in bulk water or even by simple exposure to atmospheric moisture, is a threatening process when handling boronic esters that are kinetically vulnerable to the attack of water. In fact, hydrolysis is very rapid for all acyclic boronic esters such as **27** (Figure 1.9) and for small unhindered cyclic ones such as those made from ethylene or propylene glycol (**28** and **29**) and tartrate derivatives (**36**) [114]. Catechol esters (**35**) are another class of popular derivatives as they are the direct products of hydroboration reactions with catecholborane (Section 1.3.4.4). Due to the opposing conjugation between the phenolic oxygens and the benzene ring, these derivatives are more Lewis acidic and are quite sensitive to hydrolysis. They are stable only in nonhydroxylic solvents and are not compatible with silica chromatography [115]. In the hydrolytic cleavage of catechol boronic esters, it is often necessary to carefully monitor the pH and buffer the acidity of the released catechol.

In contrast, hydrolysis can be slowed down considerably in the case of hindered cyclic aliphatic esters such as the C2-symmetrical derivatives **37** [116] and **38** [117], pinacol (**30**) [107], pinanediol (**39**) [118], Hoffmann's camphor-derived diols (**40** and **41**) [119], and the newer **42** [120] (Figure 1.9). Indeed, many of these boronic esters tend to be stable to aqueous workups and silica gel chromatography. The robustness of the esters of *trans*-1,4-dimethoxy-1,1,4,4-tetraphenyl-2,3-butanediol (**42**) was demonstrated in its applications as a protecting group for alkenylboronic acids [120].

The resulting alkenylboronic esters are tolerant of a wide variety of reaction conditions (Section 1.3.8.6). Unfortunately, the bulky boronic esters **39–42** are very robust to hydrolysis, and their conversion back to boronic acids is notoriously difficult. The removal of the bulky pinanedioxy group in boronates **39** exemplifies the magnitude of this particular problem. It is generally not possible to cleave a pinanediol ester quantitatively in water even under extreme pH conditions. It can be released slowly (over several days) and rather ineffectively by treatment with other rigid diols in chloroform [121]. Cleavage of various pinanedioxy boronates has been achieved by transborylation with boron trichloride [22, 121–125], which destructs the pinanediol unit, or by reduction to the corresponding borane using lithium aluminum hydride (Equations 1.16 and 1.17, Figure 1.12) [126]. Both of these derivatives can be subsequently hydrolyzed to afford the desired boronic acid. More recently, mild approaches have been developed to convert the robust DICHED, pinacol, and pinanediol esters into difluoroboranes or trifluoroborate salts (Equation 1.18, Figure 1.12) [127, 128]. The latter can then be hydrolyzed to the corresponding boronic acids using various methods (Section 1.2.3.8) [128, 129]. Two-phase transesterification procedures with polystyrylboronic acid [130] or with phenylboronic acid have been described, but the latter is only applicable to small, water-soluble boronic acids [131]. Most of these procedures, such as the BCl_3-promoted method, were applied to the particular case of pinanediol esters of α-acylaminoalkylboronic acids [22, 125]. Using such a substrate, **46**, an oxidative method allowed the recovery of free boronic acid **47** in good yield from a periodate-promoted cleavage that destructs the pinanediol unit or by using the biphasic transesterification method in hexanes/water (pH 3) (Equations 1.19 and 1.20, Figure 1.12) [132]. The cleavage of methoxyphenyl-substituted pinacol-like boronates **31** (Figure 1.9) can be effected under oxidative conditions, providing an orthogonal strategy to protect boronic acid compounds in various transformations [133].

Long ago, the hydrolysis of a series of five-, six-, and seven-membered phenylboronic esters was studied by measuring the weight increase of samples subjected to air saturated with water vapor (i.e., under neutral conditions) [134]. The occurrence of hydrolysis was confirmed by the observation of phenylboronic acid deposits. This early study confirmed that hindered esters such as phenylboron pinacolate (PhBpin) hydrolyze at a much slower rate, and that six-membered boronates are more resistant to hydrolysis than the corresponding five-membered analogues. These results were interpreted in terms of the relative facility of boron–water complexation to form a tetracoordinate intermediate. Two factors were proposed: (1) the increase of steric effects on neighboring atoms upon formation of the hydrated complex, and (2) the release of angle strain, which is optimal in the five-membered boronates due to the decrease of the O–B–O and B–O–C bond angles from about 120° to 109° upon going from a planar configuration to the tetracoordinate hydrated form with tetrahedral B and O atoms. Propanediol derivative **34** emphasizes the importance of steric hindrance to the coordination of water in order to minimize kinetic hydrolysis. The hydrolysis of **34** is considerably slower compared to the unsubstituted 1,3-propanediol ester (**29**). The superior stability of ester **34** toward hydrolysis was attributed to the axial

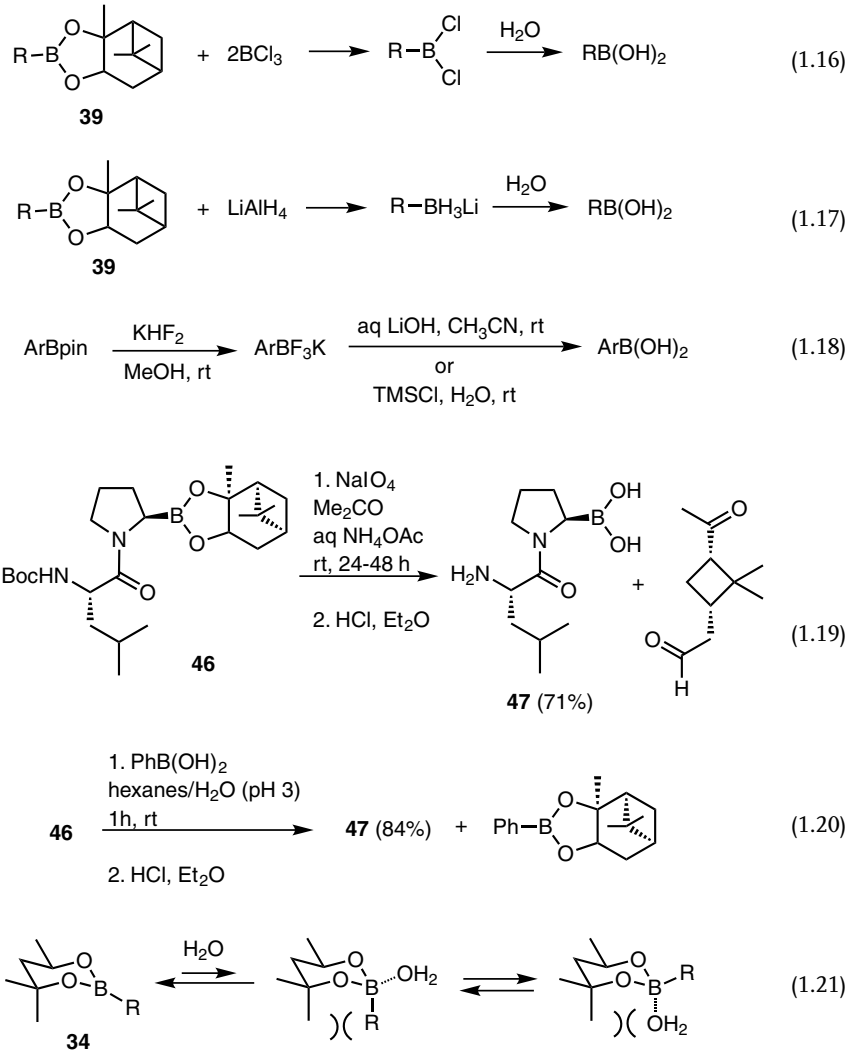
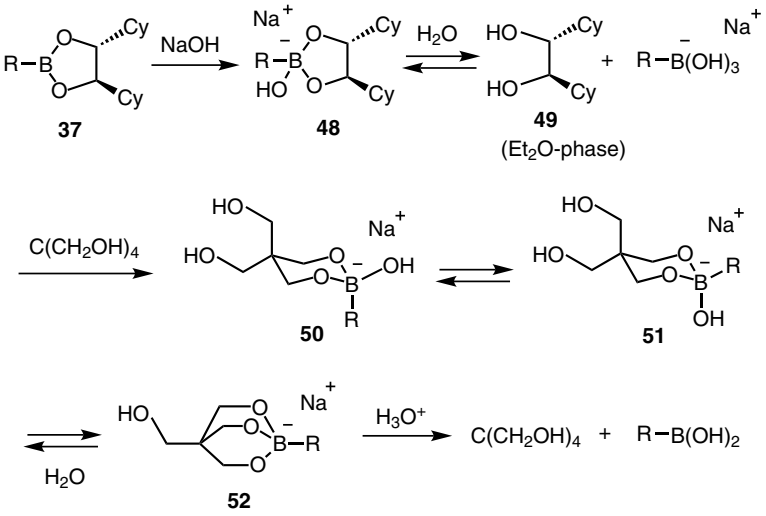


Figure 1.12 Cleavage of pinanediol boronic esters.

methyl groups, which develop a 1,3-diaxial interaction with the boron center in the approach of water from either face (Equation 1.21, Figure 1.12).

While developing a novel two-phase system for the basic hydrolysis of DICHED esters, **37**, Matteson proposed a useful generalization on the process of thermodynamic hydrolysis of boronic esters (Scheme 1.1) [135]. Using a relatively dilute nonmiscible mixture of 1 M aqueous sodium hydroxide and diethyl ether (required to avoid precipitation of boronate salt **48**), the equilibrium ratio of 42 : 1 of **49** to **37** in the ether phase was reached slowly only after 18 h by using a large excess of sodium hydroxide with respect to the boronic ester **37**. By using soluble triols like



Scheme 1.1 Hydrolysis of boronic esters in a two-phase system.

pentaerythrol to transesterify salt **48** into a more water-soluble salt (i.e., **50**/**51**/**52**) and thus facilitate the liberation of DICHED, a higher ratio of 242 : 1 was obtained. The free boronic acid could then be recovered by acidification of the aqueous phase containing a mixture of **50**–**52**, followed by extraction with ethyl acetate. This new procedure, however, was not successful for the complete hydrolysis of pinanediol phenylboronic ester, providing the optimal pinanediol:boronic ester ratio of only 3.5 : 1 in the ether phase. These results were interpreted in terms of the determining thermodynamic factors controlling the reversible hydrolysis or transesterification of boronic esters. Entropic factors in the hydrolysis of cyclic esters are unfavorable as three molecules are converted into only two. In this view, transesterification with a diol, instead of hydrolysis, is entropically even and thus more favorable. More important factors affecting the equilibrium are the effect of steric repulsions on enthalpy and the entropies of internal rotation of the free diols. For example, *trans*-4,5-disubstituted dioxaborolanes such as DICHED esters present a minimal extent of steric repulsions as the two cyclohexyl substituents eclipse C−H bonds. On the contrary, pinacol esters present a significant amount of steric repulsion from the four eclipsing methyl groups. Consequently, it is not surprising that pinacol esters can be transesterified easily with *trans*-DICHED so as to relieve these eclipsing interactions [15, 136]. In this scenario, the exceptional resistance of pinanediol esters to thermodynamic hydrolysis would be due to the rigid cyclic arrangement, whereby the two hydroxyls are preorganized in a coplanar fashion to form a boronic ester with essentially no loss of entropy from internal rotation compared to the free pinanediol. Other types of esters, including DICHED [137] and the robust pinacol esters of peptidyl boronates [138], have also been converted to the boronic acids through transesterification with diethanolamine in organic solvent, followed by acidic aqueous hydrolysis. This method, however, is effective only if the resulting

diethanolamine ester crystallizes from the solution so as to drive the equilibrium forward. As stated above, the transesterification of cyclic boronic esters with diols is often slow, and particularly so in organic solvents. Wulff *et al*. found that a number of boronic acids possessing proximal basic atoms or substituents (e.g., **16**, Figure 1.7) lead to a large neighboring group effect, and the transesterification equilibriums are reached much faster with these boronic acids as a result of a rapid proton transfer [139].

1.2.3.2.3 **Boronic Acid–Diol (Sugar) Equilibrium in Water and Protic Solvents** The reversible formation of boronic esters by the interaction of boronic acids and polyols in water was first examined in the seminal study of Lorand and Edwards [52]. This work followed an equally important study on the elucidation of structure of the borate ion [140]. By measuring the complexation equilibrium between several model diols and monosaccharides using the method of pH depression, it was shown that ester formation is more favorable in solutions of high pH where the boronate ion exists in high concentrations (Equation 1.22, Figure 1.13). This study also confirmed the Lewis acid behavior of boronic acids and the tetracoordinate structure of their conjugate base, that is, the hydroxyboronate anion (Section 1.2.2.4). Another conclusion made from this study is the lower Lewis acid strength of free boronic acids compared to that of their neutral complexes with 1,2-diols. For example, the pK_a of $PhB(OH)_2$ decreases from 8.8 to 6.8 and 4.5 upon formation of cyclic esters with glucose and fructose, respectively [141]. To explain the favorable thermodynamic effect observed at high pH (Equation 1.22, Figure 1.13) in comparison to neutral pH (Equation 1.23), it was hypothesized that the formation of hydroxyboronate complexes of 1,2-diols is accompanied by a significant release of angle strain resulting from the rehybridization of the boron from sp^2 to sp^3 (i.e., 120° versus 109° bond angles) [52]. A series of investigations on the equilibria and mechanism of complexation between boric acid or boronic acids with polyols and other ligands in water were reported by Pizer and coworker. Early work by this group [58] and others [142] showed that the stability constants of complexes increase when the aryl substituent on the boronic acid is electron poor, which is consistent with the view that the formation of anionic hydroxyboronate complexes is the drive for release of angle strain. Using methylboronic acid and simple 1,2- and 1,3-diols, equilibrium

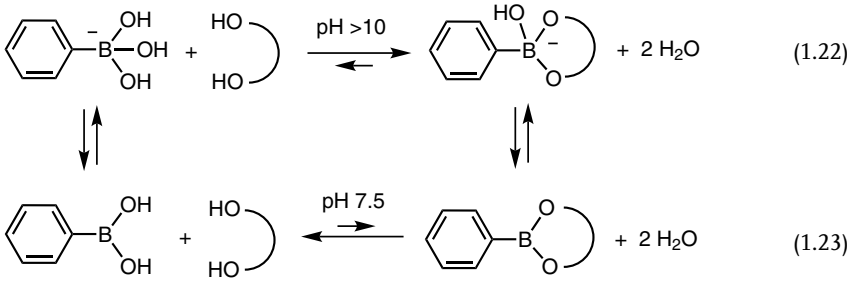


Figure 1.13 Equilibrium formation of boronic esters from diols at high (Equation 1.22) and neutral (Equation 1.23) pH in water.

constants were measured both by pH titration and ^{11}B NMR spectroscopy [143]. Constants of 2.5, 5.5, and 38 were found for 1,3-propanediol, 1,2-ethanediol, and 1,2,3-propanetriol respectively, with the latter binding much preferentially with a 1,2-diol unit. The results of this work also suggested that the tetracoordinate hydroxyboronate anion is much more reactive than the trigonal neutral boronic acid in forming esters with diols (at least 10^4 times faster), with forward rate constants in the range of 10^3–10^4 M/s. It was suggested that the high reactivity of the boronate anion could be interpreted in terms of an associative transition state involving proton transfer and hydroxide displacement within a pentacoordinated boron. This fundamental view has been challenged in a recent experimental study claiming that boronate formation with aliphatic diols occurs through trigonal boronic acids, with a high pH needed only to provide a small but sufficient concentration of the anionic, monodeprotonated diol [144]. In the past decade, interest in the interaction between boronic acids and *cis*-diols has developed tremendously due to its applications in the development of receptors and sensors for saccharides and in the design of new materials (Sections 1.6.4 and 1.6.10 and Chapters 13 and 14). For instance, the reversibility of boronic ester formation in hydroxylic solvents has been exploited in the crystallization-induced dynamical self-assembly between tetraol **53** and *p*-phenyldiboronic acid (Figure 1.14) [145]. Different inclusion complexes are observed depending on the solvent composition and the presence or absence of methanol is utilized as an *on/off* switch. For example, the [2 + 2] boxed toluene complex **54**, structurally characterized by X-ray crystallography, is formed in toluene, whereas a [3 + 3] box is formed in benzene. Similar to the case of simple polyols discussed above, the binding of carbohydrates to boronic acids is subject to the same geometrical preference for a preorganized, coplanar diol unit. In fact, it was demonstrated that in water, boronic acid receptors bind to glucose in the furanose form, which presents a very favorable, coplanar 1,2-diol [146]. X-ray crystallographic structures of 2 : 1 complexes between phenylboronic acid and D-fructose and D-glucose (in its furanose form), respectively, have been obtained [147, 148]. All these observations

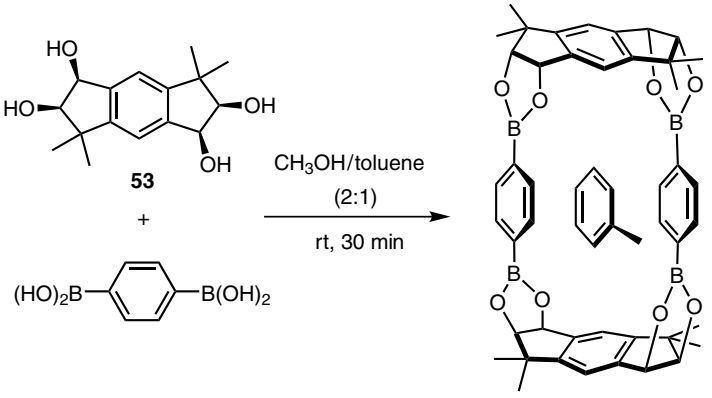
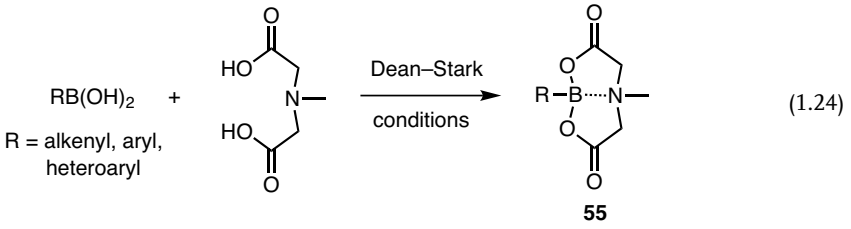


Figure 1.14 Self-assembled, reversible tetraboronic ester cages.

concur with the absence of appreciable complexation between normal boronic acids and nonreducing sugars (glycosides) and the low affinity of 1–4 linked oligosaccharides such as lactose [149, 150]. Recently, however, benzoboroxoles such as **8** (Figure 1.2) were demonstrated to complex glycopyranosides weakly [151] and these units have been employed in the design of "synthetic lectins" (Chapter 13). Fluorescent catechol derivatives such as the dye alizarin red S (ARS) also form covalent adducts with boronic acids in water, and this equilibrium has been used as a competitive color- and fluorescence-based assay for both qualitative and quantitative determination of saccharide binding [152]. Using the ingenious ARS assay, Springsteen and Wang presented an interesting cautionary tale from discrepancies found in the measurements of boronic acid–diol binding constants based on the above-mentioned method of pH depression [141]. The latter method may not always be reliable at providing the true overall equilibrium constants due to the multiple states of ionization of the boronic acid and the resulting ester (neutral trigonal or tetrahedral hydroxyboronate), which is further complicated by the pronounced effect of the solvent, pH, and buffer components and the concentration of these species on the equilibrium [141, 153]. A follow-up study further concluded that despite some accepted generalizations, exceptions exist and the optimal pH for diol–boronic acid complexation is not always above the pK_a of the boronic acid [57]. Likewise, boronic acids with a lower pK_a do not always show greater binding affinity to diols.

1.2.3.3 Acyloxy- and Diacyloxyboronates

Acyloxyboronates have seldom been employed as boronic acid derivatives compared to diacyloxyboronates [154]. *N*-Alkyliminodiacetate complexes of boronic acids homologous to **44** (Figure 1.9) were found to be even more robust than diethanolamine complexes (B−N $\Delta G^{\neq} > 90$ versus 60 kJ/mol for **43**) [20]. Compared to the alkoxy groups of **43**, the electronic effect of the carboxyl groups leads to a more acidic boron atom, hence a stronger B−N interaction. The *N*-methyl derivatives **55** (Equation 1.24), termed MIDA boronates, form easily in benzene–DMSO mixtures with a Dean–Stark apparatus and can be cleaved relatively easily in basic media [155]. MIDA boronates tolerate various reaction conditions and have recently been exploited as a means to mask boronic acids in iterative cross-coupling strategies (Section 1.3.8.6) [156].



55 (1.24)

1.2.3.4 Dialkoxyboranes and Other Heterocyclic Boranes

Several cyclic dialkoxyboranes such as 4,4,6-trimethyl-1,3,2-dioxaborinane **56** [157], 1,3,2-benzodioxaborole (catecholborane) **57** [158], and pinacolborane **58** [159] have been described (Figure 1.15). Dialkoxyboranes can be synthesized simply by the

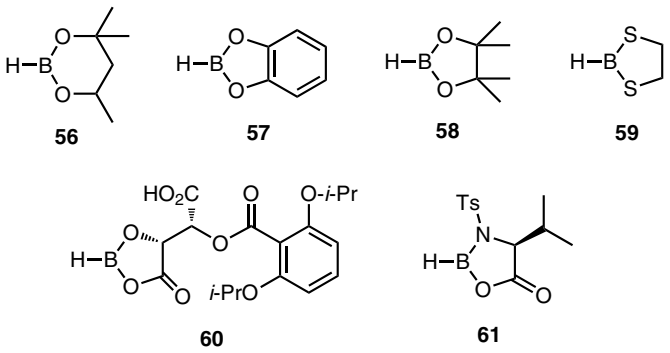


Figure 1.15 Common dialkoxyboranes and heterocyclic analogues.

reaction between equimolar amounts of borane and the corresponding diols. These borohydride reagents have been employed as hydroborating agents, in carbonyl reduction and more recently as boronyl donors in cross-coupling reactions. Dialkoxyboranes have also been invoked as intermediates in the intramolecular, alkoxy-directed hydroboration of β,γ-unsaturated esters [160]. Sulfur-based heterocyclic boranes were reported, including 1,3,2-dithiaborolane **59** [161]. Acyloxyboranes such as Yamamoto's tartaric acid-derived CAB catalyst **60** [162] and related oxazaborolidinones such as **61**, derived from *N*-sulfonylated amino acids, have been used as chiral promoters for cycloadditions and aldol reactions of silyl enol ethers [163]. Synthetic applications of these catalysts are described in Chapter 12.

1.2.3.5 **Diboronyl Esters**

A number of synthetically useful diboronyl esters such as B_2cat_2 **62** and particularly B_2pin_2 **63** have been described (Figure 1.16) [164]. The mixed reagent **64** has been reported recently and employed in regioselective alkyne diborations [165]. Reagent **63** is commercially available at a relatively low cost. Diboronyl esters can be prepared by condensation of a diol with tetrakis(dimethylamino)diboron precursor, which can be made in three steps from boron tribromide [166]. A shorter and more practical synthesis of B_2cat_2 was described [167]. The discovery that diboronyl compounds can be employed with transition metal catalysts in a variety of efficient cross-coupling and direct addition reactions to unsaturated compounds and C–H bonds can be considered one of the most significant advances in boronic acid chemistry in the past 15 years. The chemistry of diboronyl compounds has been reviewed regularly [164] and is discussed in several sections of this chapter and also in Chapters 2 and 3.

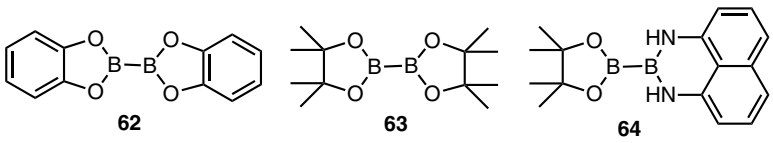


Figure 1.16 Common diboronyl reagents.

1.2.3.6 Azaborolidines and Other Boron–Nitrogen Heterocycles

A large number of heterocyclic derivatives of boronic acids have been described, and useful X-ray crystallographic data were obtained for many of these compounds. It is beyond the scope of this chapter to present a comprehensive account of these derivatives; thus, only representative examples will be described in this section (Figure 1.17). The benzodiazaborole products (**65**) of 1,2-phenylenediamine and free boronic acids form readily in refluxing toluene [168, 169]. Both aliphatic and aromatic acids are applicable, and it was claimed that the resulting adducts are easier to recrystallize than the diethanolamine boronates. An intramolecular adduct was also reported [170]. These benzodiazaboroles are air-stable, and the adduct of phenylboronic acid was found to hydrolyze only slowly in aqueous solutions. With anhydrous hydrogen chloride in toluene, a dihydrochloride salt was formed [168, 169]. The unusual stability of adducts **65** was further supported by the fact that

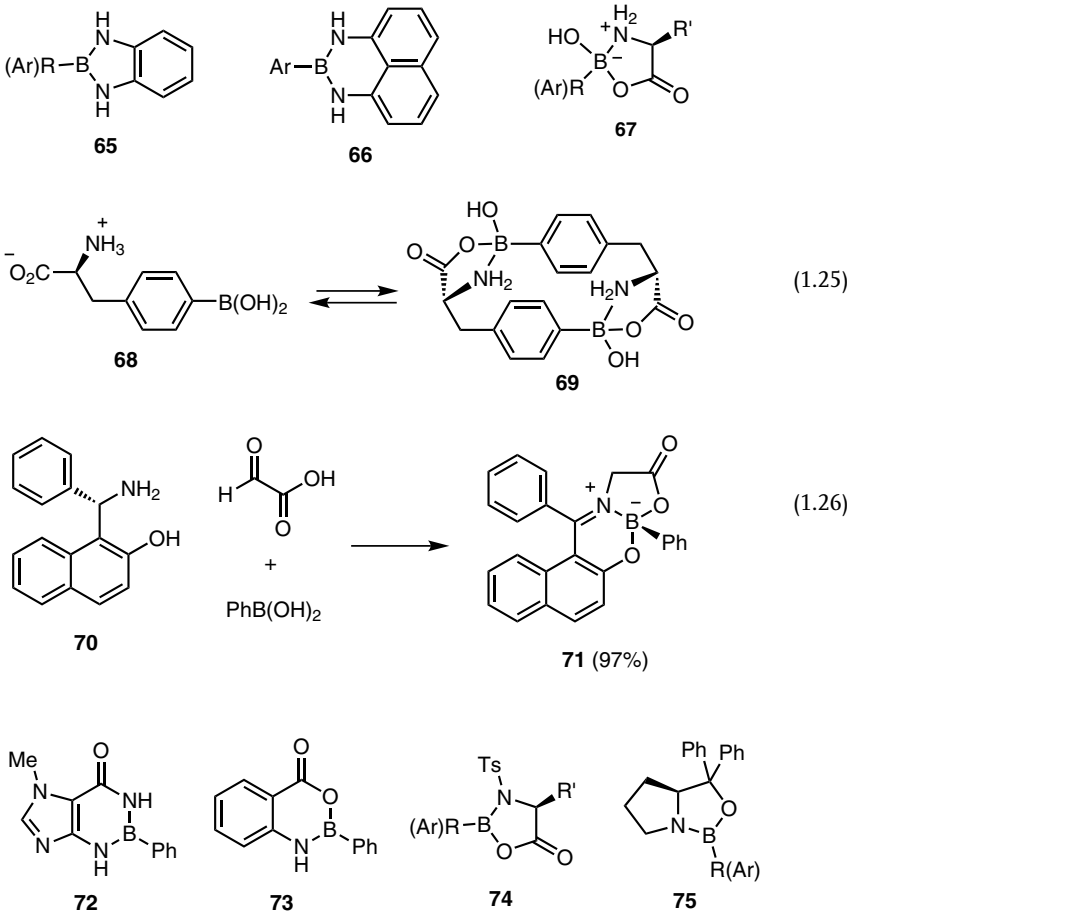
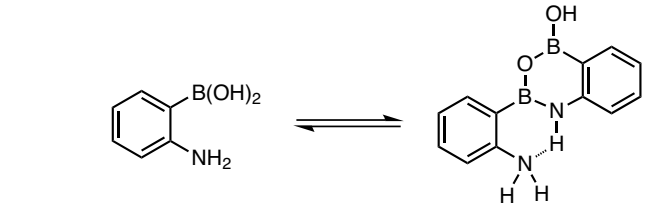


Figure 1.17 Examples of azaborolidines and other heterocyclic analogues.

they even form by exchange of tartrate esters with 1,2-phenylenediamine at room temperature in benzene. Control studies showed that the position of the equilibrium lies much toward the diazaborole, which is surprising with respect to thermodynamic factors such as the much higher energy of covalent B–O bonds compared to B–N bonds (see Section 1.2.2.1). As both ethylenediamine and aniline itself did not form similar covalent adducts under the same conditions, it was suggested that the favorable geometry of 1,2-phenylenediamine and the stability of the resulting five-membered ring and its partial aromatic character were responsible for the highly favorable formation of adducts **65** [168]. The 1,8-diaminonaphthalene adducts **66** form readily in refluxing toluene, are cleaved with aqueous acid, and have been exploited recently as boronic acid masking groups in iterative cross-coupling (see Section 1.3.8.6) [171]. Diazaborolidines from aliphatic 1,2-diamines, on the other hand, are not prepared with such ease. For example, a number of chiral ones evaluated as chiral proton sources were prepared from dichloroboranes [172].

Amino acids can condense with boronic acids to form 1 : 1 chelates of type **67** [173]. The tetracoordinate structure of these adducts is very apparent by NMR due to the formation of a new stereocenter at boron. Interestingly, 4-boronophenylalanine (**68**), a potential BNCT agent, was shown to dimerize to form head-to-tail paracyclophane derivative **69** in a reversible fashion in DMSO (Equation 1.25, Figure 1.17) [174]. This dimer is prevalent at low concentrations (<50 mM), while oligomeric mixtures predominate at higher concentrations. Amino acid adducts of boronic acids are hydrolytically unstable, and **69** was indeed found to revert to free **68** upon addition of water to the solution. In contrast, the optically pure internally coordinated monomer **71** (Equation 1.26, Figure 1.17) is stable [24]. It was prepared in optically pure form from amino alcohol **70** through a remarkable C–to–B chirality transfer process via a 1,3 H-shift. Purine analogue **72** was found to hydrolyze readily in aqueous ethanolic solutions [175]. The addition product **73** between anthranilic acid and phenylboronic acid was also reported [176]. Salicylhydroxamic acid adducts of arylboronic acids are more resistant to hydrolysis and were proposed as components of an affinity system for bioconjugation (Section 1.6.8) [177]. Both B-alkyl and B-aryl oxazaborolidinones **74**, made from *N*-sulfonylated amino acids such as tryptophan, have been employed as chiral Lewis acids in several synthetic transformations (Chapter 12) [178] and in crystallization-induced asymmetric transformations [179]. Amino alcohols can form oxazaborolidines by condensation with boronic acids under anhydrous conditions. Chiral oxazaborolidines derived from reduced amino acids (e.g., **75**) have been a popular class of Lewis acids for cycloadditions [180] and as catalysts and reagents for the enantioselective reduction of ketones and imine derivatives [181]. The analogous cationic oxazaborolidinium catalysts are even more efficient (see Chapter 12) [182].

ortho-Aminophenylboronic acid exists as a hydrogen-bonded heterodimer in anhydrous aprotic solutions (Equation 1.27, Figure 1.18) [183]. In addition to the benzoboroxole described in Section 1.2.2.1 (**8**, Figure 1.2) [16, 184, 185], there are several other examples of internal heteroaromatic boronic acid derivatives where an *ortho*-substituent closes onto the boron atom with either a dative or a covalent bond [186]. For example, *ortho*-anilide derivatives **76** and the corresponding ureas (**77**), of putative internally chelated form **A**, were shown to exist mainly in their cyclic



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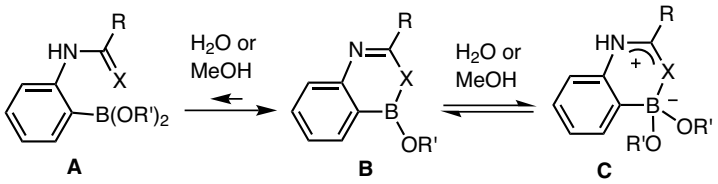


(1.28)

76 X = O,
77 X = NH, NR
R = H, NH_2, alkyl or aryl
R' = H , CH_3, or CMe_2CMe_2

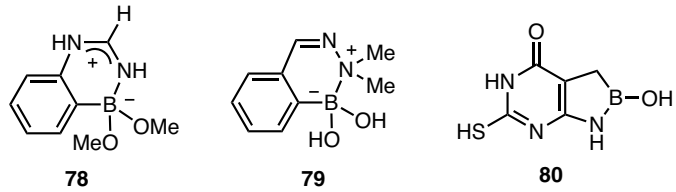


Figure 1.18 Hemi-heterocyclic boronic ester derivatives.

monodehydrated form **B** (Equation 1.28, Figure 1.18) [183]. This is probably true even in aqueous or alcohol solutions owing to the partial aromatic character of these boron-containing analogues of purine heterocycles. In fact, it has even been shown that these and similar compounds can add one molecule of water or alcohol by 1,4-addition and thus exist in equilibrium with form **C**. One such derivative **78** was obtained from recrystallization in methanol, and the X-ray crystallographic analysis proved its zwitterionic structure with a tetrahedral boronate anion. A class of related derivatives made from 2-formylboronic acid and hydrazines was also characterized [186], and the boroxine of one internally chelated derivative **79** was studied by X-ray crystallography [187]. Other examples of heterocyclic derivatives include pyrimidine analogue **80** [188].

1.2.3.7 **Dihaloboranes and Dihydroalkylboranes**

The highly electrophilic dihaloboranes can undergo reactions that do not affect boronic acids and esters. For example, to achieve an oxidative amination of the B–C bonds in boronate derivatives, it is necessary to transform boronic esters into the corresponding dichlorides (Section 1.5.2.2). Several methods have been described for the preparation of alkyl- and aryl- dichloroboranes, but only a few of those conveniently employ boronic acids and esters as substrates. They can be

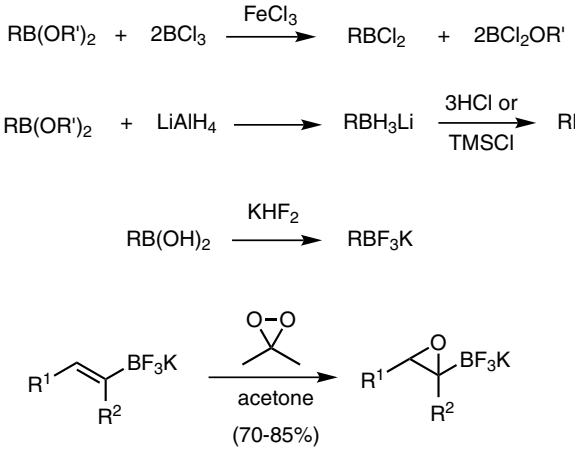


Figure 1.19 Synthesis of dichloroboranes, monoalkylboranes, and trifluoroborate salts.

accessed either by iron trichloride-catalyzed exchange of the boronic ester with BCl_3 (Equation 1.29, Figure 1.19) [189] or by treatment of the corresponding monoalkylborane with TMSCl [190] or acidification with anhydrous HCl in dimethyl sulfide (Equation 1.30) [191]. The requisite monoalkyl and monoaryl borohydride salts can be made by treating boronic esters with $LiAlH_4$ [192], and the use of HCl in dimethyl sulfide leads to the isolation of the stable $RBCl_2$–SMe_2 adducts (Equation 1.30) [191]. Both of these methods can be performed without any detectable epimerization when using chiral boronic esters originating from the asymmetric hydroboration of alkenes [189, 191].

1.2.3.8 **Trifluoro- and Trihydroxyborate Salts**

The organotrifluoroborate salts discussed in Section 1.2.3.2.2 are a class of air-stable boronic acid derivatives that can be easily prepared according to a procedure described by Vedejs *et al.* (Equation 1.31, Figure 1.19) [193]. Boronic esters also react to give the desired salts [127]. These crystalline derivatives are easy to handle, are competent substrates in many of the same reactions that employ free boronic acids, and often outperform boronic acids as cross-coupling reagents. Chapter 11 provides an overview of their synthetic applications in transition metal cross-coupling reactions and other transformations [194]. They have also been evaluated as tracer molecules for positron emission tomography (PET) applications [195]. There are several methods to hydrolyze trifluoroborate salts back to boronic acids (see Chapter 11) and they can also be conveniently transformed into dichlororoboranes by treatment with $SiCl_4$ in THF [196]. The incompatibility of boron–carbon bonds with several oxidants limits the ability to further transform compounds containing a boronic acid (ester) functionality. Taking advantage of the strong B—F bonds, the use of organotrifluoroborate salts may be viewed as a way to protect boron's vacant orbital against an electrophilic reaction with a strong oxidant. Thus, as described in Chapter 11, organotrifluoroborate salts have been shown to tolerate oxidations,

including the remarkable epoxidation of 1-alkenyltrifluoroborate salts with preservation of the carbon–boron bonds in good yields with dimethyldioxirane (Equation 1.32, Figure 1.19) [197]. It is significant that under the same conditions, 1-alkenylboronic acids and the corresponding pinacol esters rather lead to the corresponding aldehyde resulting from B–C bond oxidation. Owing to their unique properties, interest in the chemistry of trifluoroborate salts has grown tremendously and several hundreds have become commercially available.

Although they have long been postulated to exist in basic aqueous solutions, trihydroxyborate salts of boronics are discrete, isolable derivatives that had not been characterized until recently [23]. The sodium salt of *p*-methoxyphenyl boronic acid (**11**, Figure 1.2) was recrystallized in water and its X-ray crystallographic structure elucidated. When concentrated NaOH is added, these borate salts precipitate from organic solutions and they can be isolated through a simple filtration. Not surprisingly, they can undergo Suzuki–Miyaura cross-coupling in the absence of an added base [23]. Cyclic trialkoxyborate salts (made from triols) behave similarly [198].

1.3
Preparation of Boronic Acids and Their Esters

The increasing importance of boronic acids as synthetic intermediates in the past decades has motivated the development of new, mild, and efficient methods to provide access to these important compounds. Of particular interest is the synthesis of arylboronic acids substituted with a wide range of other functional groups. As a consequence of their growing popularity and advances in methods available for their preparation, a few thousands of functionalized boronic acids have become available from several commercial sources. Although a number of methods like the oxidation or hydrolysis of trialkylboranes bear a significant historical and fundamental relevance, this section is devoted mainly to modern methods of practical value for synthetic chemists.

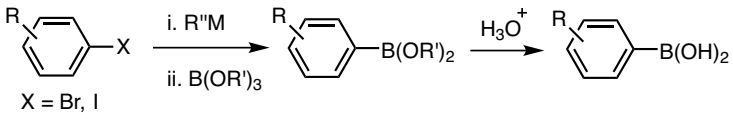
1.3.1
Arylboronic Acids

Arylboronic acids remain the most popular class of boronic acids. Their popularity in medicinal chemistry is in large part due to their role as cross-coupling partners for the synthesis of biaryl units (Section 1.5.3.1), which are present in the structure of several pharmaceutical drugs. Several methods, summarized in a generic way in Figure 1.20, are now available for the synthesis of complex arylboronic acids and the following section provides an overview of these methods with selected examples highlighted in Table 1.3.

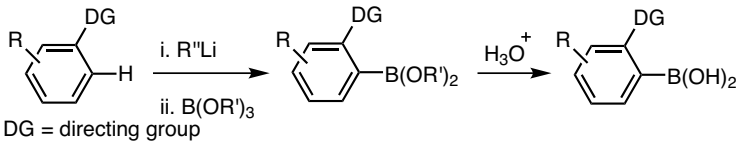
1.3.1.1 Electrophilic Trapping of Arylmetal Intermediates with Borates

One of the first and probably still the most common way of synthesizing arylboronic acids involves the reaction of a hard organometallic intermediate (i.e., lithium or

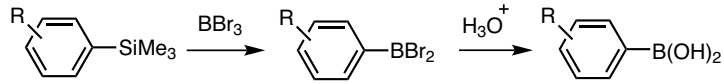
1.3.1.1.1 Electrophilic borate trapping of arylmetal intermediates from aryl halides



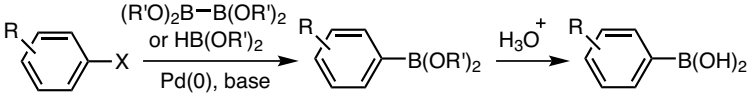
1.3.1.1.2 Electrophilic borate trapping of arylmetals from directed ortho-metallation



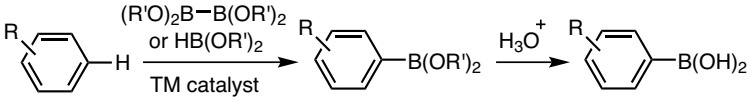
1.3.1.2 Transmetallation of arylsilanes and arylstannanes



1.3.1.3 Transition metal-catalyzed coupling between aryl halides/triflates and diboronyl reagents



1.3.1.4 Direct boronation by transition metal-catalyzed aromatic C–H functionalization



1.3.1.5 Cycloadditions of alkynylboronates followed by aromatization

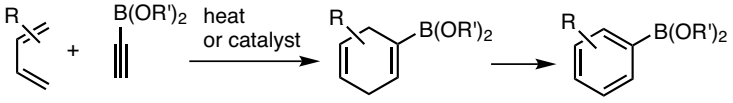
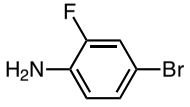
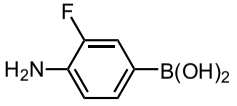
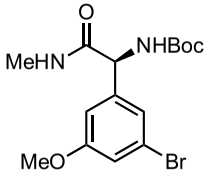
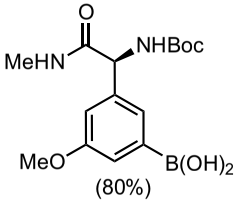
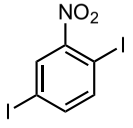
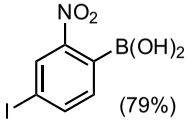
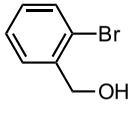
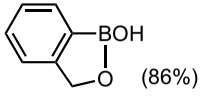


Figure 1.20 Common methods for the synthesis of arylboronic acids (esters).

magnesium) with a borate ester at a low temperature, which is necessary to minimize double addition leading to borinate side product. The corresponding zinc and cadmium species are much less effective [199].

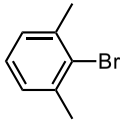
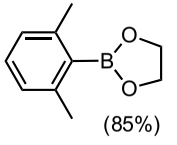
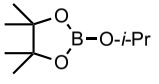
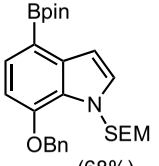
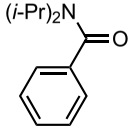
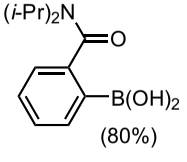
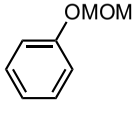
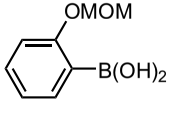
1.3.1.1.1 **By Metal–Halogen Exchange with Aryl Halides** Provided that the aryl halide substrate is compatible with its transformation into a strongly basic and nucleophilic arylmetal reagent, relatively simple aryl, alkenyl, and even alkylboronic acids can be made from a sequence of metal–halogen exchange followed by electrophilic trapping with a trialkylborate. The first such methods for preparing phenylboronic acid, which

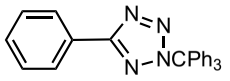
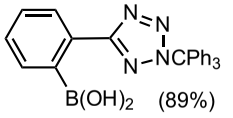
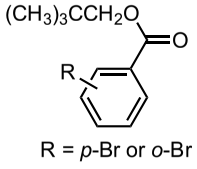
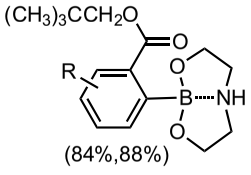
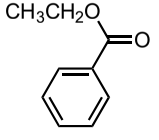
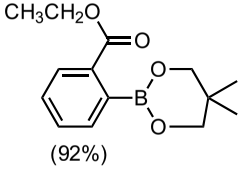
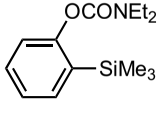
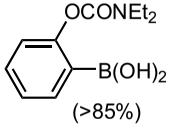
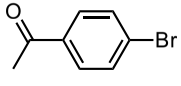
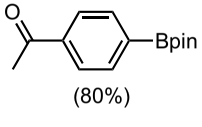
Table 1.3 Selected examples of preparative methods for arylboronic acids and esters.

Entry	Substrate	Conditions	Product	Reference
1		1. i. *n*-BuLi (2 equiv), THF, 0 °C ii. TMSCl (2 equiv) 2. i. *t*-Buli (2.2 equiv) Et_2O, −78 °C ii. $B(OMe)_3$ (xs), −78 °C iii. 0.1N aq HCl	 (45%)	[210]
2		i. MeMgCl (5 equiv), THF, 0 °C ii. *t*-BuLi (5 equiv), −78 °C iii. $B(OMe)_3$ (10 equiv), 0 °C	 (80%)	[211]
3		i. PhMgCl (1.1 equiv), THF, −60 °C ii. $B(OMe)_3$, 0.5 h, −60 °C iii. 2M HCl, −20 °C	 (79%)	[214]
4		i. *n*-BuLi (2 equiv) Et_2O, 0 °C, 2 h; −78 °C ii. $B(OMe)_3$ (1 equiv) iii. aq HCl	 (86%)	[16]

(*Continued*)

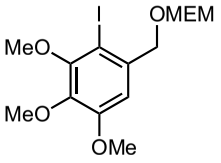
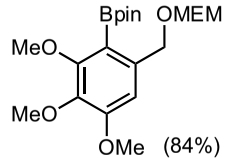
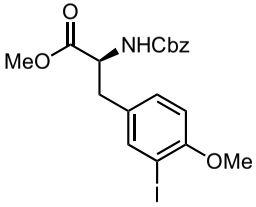
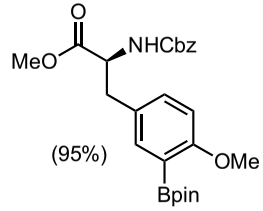
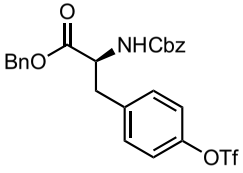
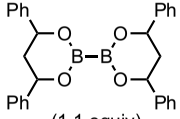
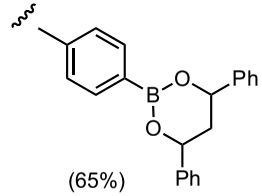
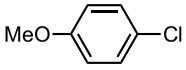
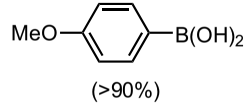
Table 1.3 *(Continued)*

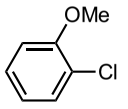
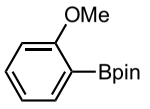
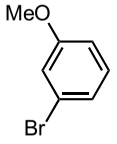
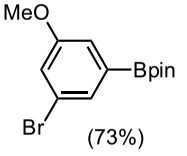
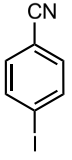
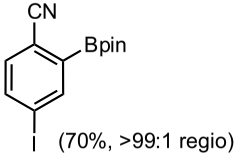
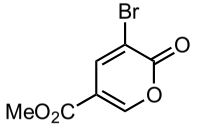
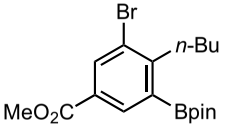
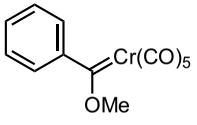
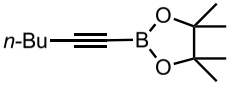
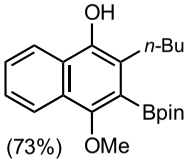
Entry	Substrate	Conditions	Product	Reference
5		i. *i*-PrMgBr, THF, −40 °C ii. $B(OMe)_3$, THF, −78 °C iii. $HOCH_2CH_2OH$, toluene	 (85%)	[215]
6		i. *t*-BuLi, THF, −78 °C ii. 	 (68%)	[216]
7		i. *s*-BuLi, TMEDA THF, −78 °C ii. $B(OMe)_3$ ii. 5% aq HCl	 (80%)	[221]
8		i. *s*-BuLi, TMEDA THF, −78 °C ii. $B(OMe)_3$ ii. 5% aq HCl		[222]

9		i. *n*-BuLi (1 equiv) THF, ≤20 °C ii. B(O-*i*-Pr)$_3$ (1.3 equiv) ii. *i*-PrOH-NH_4Cl-H_2O		[224]
10		i. LDA (1.2 equiv) B(O-*i*-Pr)$_3$ (2.6 equiv), THF ii. Diethanolamine (1.1 equiv)		[226]
11		i. LTMP (1.5 equiv) B(O-*i*-Pr)$_3$ (2 equiv) THF, −78 °C ii. $HOCH_2CMe_2CH_2OH$		[227]
12		i. BBr_3 (1.5 equiv) CH_2Cl_2, −78 °C to rt ii. 5% aq HCl		[222]
13		B_2pin_2 (1.1 equiv) $PdCl_2$(dppf) (3 mol%) KOAc (3 equiv) DMSO, 80 °C, 1 h		[232]

(*Continued*)

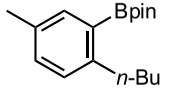
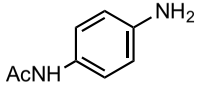
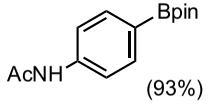
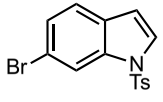
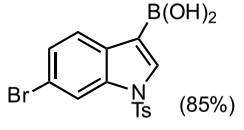
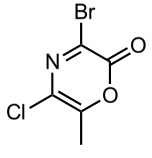
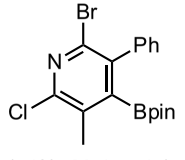
Table 1.3 *(Continued)*

Entry	Substrate	Conditions	Product	Reference
14		 (2 equiv) Et_3N (3 equiv) $Pd(OAc)_2$ (5 mol%) PCy_2(*o*-biph) (10 mol%) 80 °C, 0.5 h		[234]
15		B_2pin_2 $PdCl_2$(dppf) (3 mol%) KOAc (3 equiv) DMSO, 80 °C, 3 h		[237]
16		 (1.1 equiv) $PdCl_2$(dppf) (8 mol%) KOAc, DMF, 100 °C, 3 h		[240]
17		$B_2(OH)_2$ (1.5 equiv) Pd(0) (1 mol%) XPhos (2 mol%) NaO*t*-Bu (1 mol%) KOAc (3 equiv) EtOH, 80 °C, 18 h		[241]

18		B_2pin_2 (1.1 equiv) $Pd(dba)_2$ (3 mol%) PCy_3 (7.2 equiv), KOAc (1.5 equiv) dioxane, 80 °C, 48 h	 (70%)	[242]
19		B_2pin_2 (1.1 equiv) 1/2[IrCl(COD)]$_2$ + bpy (3 mol%) benzene, 80 °C, 16 h	 (73%)	[253]
20		B_2pin_2 (1.0 equiv) [Ir(OMe)(COD)]$_2$ (1.5 mol%) dtbpy (3 mol%) THF, 25 °C, 8–48 h	 (70%, >99:1 regio)	[255]
21		 o-$Cl_2C_6H_4$, 180 °C, 18 h (–CO_2)	 (82%, 10:1 regio)	[260]
22		 THF, 45 °C, 16 h	 (73%)	[261]

(*Continued*)

Table 1.3 *(Continued)*

Entry	Substrate	Conditions	Product	Reference
23		1. 1. *n*-Bu—≡—Bpin $CoBr_2$(dppe) (10 mol%) ZnI_2 (20 mol%) Zn (20 mol%) CH_2Cl_2, rt 2. DDQ, C_6H_6	 (80%, >95:5 regio)	[263]
24		B_2pin_2 *t*-BuONO $(PhCO_2)_2O$ (2 mol%) MeCN, rt	 (93%)	[264]
25		1. $Hg(OAc)_2$, AcOH H_2O, $HClO_4$ 2. BH_3-THF 3. H_2O	 (85%)	[216]
26		Ph—≡—Bpin toluene, reflux, 48 h (–CO_2)	 (74%, 20:1 regio)	[271a]

involved the addition of methylborate to an ethereal solution of phenylmagnesium bromide at −15 °C, became notorious for providing a low yield of desired product [200]. Boron trifluoride was also employed in place of borates [201]. In the early 1930s, Johnson and coworkers developed the first practical and popular method for preparing phenylboronic acid and other arylboronic acids with an inverse addition procedure meant to minimize the undesired formation of borinic acid by-product [202, 203]. In this variant, phenylmagnesium bromide is slowly added to a solution of *n*-butylborate at −70 °C. In the reaction between an arylmagnesium bromide and a trialkylborate, the exhaustive formation of undesired borinic acid and borane via a second and third displacement on the intermediate boronic ester is prevented by the precipitation of the magnesium trialkoxyphenylborate salt (**81**, M = MgX, in Equation 1.33, Figure 1.21). The latter salt is also thought not to dissociate into the corresponding boronic ester and metal alkoxide at low temperatures, which is key to protecting the desired boronate from a second displacement by the Grignard reagent (Equation 1.34). Then, the free boronic acid is obtained following a standard aqueous workup to hydrolize the labile boronic ester substituents. These types of procedures have been used successfully in the kilogram-scale preparation of arylboronic acids [204–206]. Borinic esters may form in significant amounts at higher temperatures or when using electron-rich arylmagnesium reagents. Equilibration of mixtures leading to enrichment in boronic esters is practically useful in some limited cases [84].

The isolation of free boronic acids using an aqueous workup may lead to low yields especially in the case of small or polar ones, which tend to be water soluble even at a low pH (Sections 1.2.2.2 and 1.4). In such cases, it is often better to isolate the desired compound as a boronic ester. Using an improved procedure that does not involve an aqueous workup, Brown and Cole reported that the reaction of several types of organolithium intermediates with triisopropylborate was found to be very effective for the synthesis of arylboronic esters [207]. To help minimize the possible formation of borinic acids and boranes by multiple displacements (i.e., Equation 1.34 in Figure 1.21), the Brown–Cole protocol involves the slow addition of the organolithium to a solution of triisopropylborate in diethyl ether cooled to −78 °C. The use of smaller borate esters such as trimethylborate gave large proportions of multiple addition products (i.e., borinic acid and borane). With the use of triisopropylborate, however, the clean formation of lithium alkoxyboronate salt (**81**, M = Li, R = *i*-Pr, Figure 1.21) was demonstrated by NMR spectroscopy, and the boronic ester can be

$$\mathrm{ArM} + \mathrm{B(OR)_3} \longrightarrow \underset{\mathbf{81}}{\mathrm{M[ArB(OR)_3]}} \rightleftharpoons \mathrm{ArB(OR)_2} + \mathrm{ROM} \qquad (1.33)$$

$$\mathrm{ArB(OR)_2} + \mathrm{ArM} \longrightarrow \mathrm{M[Ar_2B(OR)_2]} \rightleftharpoons \mathrm{Ar_2B(OR)} + \mathrm{ROM} \qquad (1.34)$$

Figure 1.21 Equilibrium involved in the reaction between arylmetal intermediates (Li or Mg) and borates.

obtained in high purity as the final product upon addition of anhydrous hydrogen chloride at 0 °C. The use of pinacol borates leads directly to pinacol boronates. An improvement to this procedure involves pyrolysis or the use of acid chlorides to breakdown the lithium triisopropylboronate salt, thereby avoiding the generation of free isopropanol and lithium chloride and facilitating the isolation of the boronic ester [208]. An *in situ* quench variant whereby triisopropylborate is present in the flask prior to the addition of butyllithium was described, and in many cases this simpler procedure afforded superior yields of arylboronic and heteroaryl boronic acids compared to the sequential addition procedure [209]. In addition to arylboronic esters, alkenyl, alkynyl, alkyl, and even α-haloalkylboronic esters were made in this way [207]. If desired, the free boronic acid may be obtained by hydrolysis of the ester. The metal–halogen exchange route, both from aryllithium and arylmagnesium intermediates, can even be applied to functionalized substrates containing acidic hydrogen atoms provided that temporary protection via silylation is effected (entry 1, Table 1.3) or a suitable excess of organometallic reagent is employed (entries 2 and 4). All isomers of hydroxybenzeneboronic acid were synthesized from the corresponding bromophenols using this method [212]. An efficient, low-temperature I–to–Mg exchange protocol [213] compatible with esters, nitriles, and benzylic bromide functionalities was employed in a facile synthesis of *o*-nitro arylboronic acids (entry 3, Table 1.3) [214a]. A variant using in situ borate quench provides a noncryogenic preparation of other arylboronic esters [214b].

A new convenient procedure to synthesize arylboronic esters from Grignard reagents and trimethylborate was described [215]. This method involves a nonaqueous workup procedure where the resulting solution of aryldimethoxyboronate is evaporated to eliminate the excess $B(OMe)_3$ and the residual solid is refluxed overnight in a solution of diol in toluene. In particular, several ethylene glycol arylboronic esters were prepared using this method (e.g., entry 5, Table 1.3). Alternatively, the robust pinacol ester can be obtained directly by electrophilic quench of the aryllithium intermediate with a pinacol borate ester (entry 6). The use of bis(diisopropylamino)boron chloride as trapping agent in the reaction of both organolithium and magnesium compounds provides the corresponding bis(diisopropylamino)boranes, which can be easily transformed into the corresponding boronic esters and oxazaborolidines by exchange with a diol or an aminodiol [217].

1.3.1.1.2 **By Directed ortho-Metalation** The metalation of arenes functionalized with coordinating *ortho*-directing groups such as amines, ethers, anilides, esters, amides, and carbamates is yet another popular way to access arylmetal intermediates that can be trapped with boric esters. Early work showed that the *ortho*-lithiation of *N,N*-dialkylated benzylamines was a suitable method for the synthesis of *ortho*-methylamino-benzeneboronic acids [218–220]. Sharp and Snieckus further demonstrated the efficiency of this method in the preparation of *ortho*-carboxamido phenylboronic acids (entry 7, Table 1.3) [221]. This protocol was then generalized to many other substrates. For example, methoxymethoxybenzene (entry 8) and pivaloylaniline can be treated with *s*-BuLi in the presence of TMEDA in THF at

−78 °C, and the resulting *ortho*-lithiated intermediates are quenched with trimethyl borate followed by an aqueous acidic workup described above (Section 1.3.1.1.1), giving the corresponding arylboronic acids in good yields [222, 223]. Although the crude boronic acids could be used directly in Suzuki cross-coupling reactions, they were characterized as their stable diethanolamine adducts. The *ortho*-metalation route to arylboronic acids constitutes a reliable process in pharmaceutical chemistry, where it can be applied to heterocyclic intermediates such as a tetrazole required in the synthesis of the antihypertensive drug losartan (entry 9, Table 1.3) [224]. *N,N*-Diethyl *O*-carbamates are particularly valuable directors for the introduction of *ortho*-boronyl groups, as they can also be employed as orthogonal partners in Suzuki–Miyaura cross-couplings [225]. The use of carboxyesters as directing groups is more problematic as the metalated intermediate can undergo condensation with the benzoate substrate, giving a benzophenone. In a newer protocol, the metalation step is performed in the presence of the borate electrophile [226]. This *in situ* metalation–boronylation procedure employs LDA as base, and neopentyl esters were found particularly suitable because of their stability in the presence of this base. Most importantly, the LDA is compatible with boric esters under the conditions employed, and its inertness to bromide-substituted benzoates provides another significant advantage over the use of BuLi for the deprotonation step. Thus, treatment of a solution of bromo-substituted neopentyl benzoate esters and excess triisopropylborate with LDA (1.1–1.5 equiv) in THF led to the isolation of crude *ortho*-carboxy arylboronic acids, which were isolated as diethanolamine adducts in high yields (entry 10, Table 1.3). A limitation of this method, using LDA as the base, is the requirement for an electron-withdrawing substituent to activate the arene substrate. Neopentyl benzoate, for example, does not undergo directed metalation and rather gives the corresponding diisopropyl carboxamide. A recent variant of this *in situ* trapping procedure using 2,2,6,6-tetramethylpiperidide (LTMP) as the base led to a more general methodology allowing the presence of other substituents normally incompatible with standard *ortho*-metalation procedures with alkyllithium bases [227]. For example, ethyl benzoate, benzonitrile, and fluoro- and chlorobenzene were transformed in high yield into the corresponding *ortho*-substituted boronic acids as neopentylglycol esters. As demonstrated in the case of ethyl benzoate (entry 11), the use of LTMP as the base is particularly advantageous because LDA fails to metalate this substrate and rather provides the carboxamide product of addition to the ester.

1.3.1.2 **Transmetalation of Aryl Silanes and Stannanes**

One of the earliest methods for preparing aromatic boronic acids involved the reaction between diaryl mercury compounds and boron trichloride followed by hydrolysis [228]. Borane can also be employed [229]. As organomercurial compounds are to be avoided for safety and environmental reasons, this approach has remained unpopular. In this respect, trialkylaryl silanes and stannanes are more suitable and both can be transmetalated efficiently with a hard boron halide such as boron tribromide [230]. The apparent thermodynamic drive for this reaction is the higher stability of B−C and Si(Sn)−Br bonds of product compared to the respective B−Br and Si(Sn)−C bonds in the substrates. It is noteworthy that the resulting

dibromoboranes can be cross-coupled *in situ* with aryl halides [231]. Using this ipso-desilylation method, functionalized arylboronic acids, including indolylboronic acids, can be made following an aqueous acidic workup to hydrolyze the arylboron dibromide intermediate [222, 231]. For example, some boronic acids were synthesized more conveniently from the trimethylsilyl derivative than by a standard low-temperature *ortho*-metalation procedure (entry 12, Table 1.3). The use of pinacol in the workup leads to the corresponding boronic esters [231].

1.3.1.3 Coupling of Aryl Halides with Diboronyl Reagents

The traditional method involving the trapping of aryllithium or arylmagnesium reagents with boric esters is limited by the functional group compatibility of these hard organometallic species as well as the rigorously anhydrous conditions required. In search for milder conditions amenable to a wider scope of substrates and functionalities, Miyaura and coworkers found that diboronyl esters such as B_2pin_2 (**63**, Figure 1.16) undergo a smooth cross-coupling reaction with aryl bromides, iodides, and triflates under palladium catalysis [232]. This modern reaction process is described in Chapter 2; thus, only a brief summary is presented in this section. A detailed mechanism has been proposed [164b, 232], and a number of diboronyl reagents are now commercially available, including the common diborylpinacolate (B_2pin_2). Standard conditions for the coupling reaction involve $PdCl_2$(dppf) as catalyst, with potassium acetate as the base in a polar aprotic solvent [232]. The mildness of these conditions is apparent in the use of carbonyl-containing substrates such as benzophenones (entry 13, Table 1.3) or benzaldehydes [92], which would be incompatible with the metal–halogen exchange procedures described in Section 1.3.1.1. Pinacolborane (**58**, Figure 1.15) can also serve as an efficient boronyl donor in this methodology (entry 14) [233]. The use of cedranediolborane has also been proposed as an alternative to pinacolborane, which gives pinacol esters that are notoriously difficult to hydrolyze [235]. The scope of arene substrates in coupling reactions with diboronyl esters or pinacolborane is very broad. The preparation of peptide dimers has been described using a one-pot borylation/Suzuki coupling [236]. Hindered [238], electron-rich aryl halides (entries 14 and 15), and even pyridinyl halides [239], may also be used with high efficiency. Of particular significance is the use of pinacolborane with aryltriflates, which can be made with ease from phenols [233]. For instance, 4-borono-phenylalanine is now easily accessible from tyrosine using this approach (entry 16). As shown with this example and others [238], the use of diboronyl reagents with hydrolytically labile substituents is advantageous if the desired product is the free boronic acid. Alternatively, a recent procedure employs $B_2(OH)_4$ directly with aryl halides (entry 17) [241]. Aryl chlorides are more attractive substrates compared to bromides and iodides due to their low cost and wider commercial availability. In this regard, modified conditions with $Pd(dba)_2$ and tricyclohexylphosphine as catalyst system provide pinacolates from aryl chlorides, even electron-rich ones (entry 18, Table 1.3) [242]. Other palladium ligand systems are efficient [243]. Alternatively, a microwave-promoted procedure for aryl chlorides using a palladium/imidazolium system has been described [244]. A similar procedure employed aryldiazonium salts as substrates [245]. Recent procedures for

nickel-catalyzed borylations for aryl halides [246] and sulfonates [247] and copper-catalyzed variants have been reported [248].

1.3.1.4 Direct Boronation by Transition Metal-Catalyzed Aromatic C–H Functionalization

In terms of atom economy, a very attractive strategy for preparing boronic acids and esters is the direct boronation of arenes through a transition metal-catalyzed C–H functionalization [249]. In addition to the catalyst, a suitable boron donor is required, and both diboronyl esters and dialkoxyboranes were found to be very appropriate in this role. The concept of this type of direct borylation was first demonstrated on alkanes using photochemical conditions [250]. For arene substrates, several research groups including those of Smith [251], Hartwig [252], Miyaura/Hartwig [253], and Marder [254] have pioneered a number of efficient procedures using iridium and rhodium catalysts (entry 19, Table 1.3). The most active catalyst for this chemistry is an iridium di-*t*-butylbipyridine (dtbpy) complex [253], and room-temperature borylations of *para*-substituted cyanoarenes with this system tend to occur mainly *ortho* to the nitrile (entry 20) [255]. Otherwise, regioselectivity is under steric control and it remains a major challenge except for monosubstituted and 1,3-disubstituted arenes where *meta*-borylation is the main pathway, thus complementing the directed *ortho*-metalation/borylation approach described in Section 1.3.1.2 [256]. Exceptionally, a heterogeneous, silica-supported Ir-phosphine catalyst provides directed *ortho*-borylation of a wide variety of monosubstituted arenes in very high selectivity [257]. The scope and mechanism of this contemporary approach to the synthesis of boronic acid derivatives are discussed in detail in Chapter 2.

1.3.1.5 Cycloadditions of Alkynylboronates

Alkynylboronates are versatile cycloaddition partners [258]. Thermal [4 + 2] cycloadditions are possible with activated dienes [259, 260]. For example, 2-pyrones provide polysubstituted arylboronates in variable regioselectivities following CO_2 extrusion (entry 21, Table 1.3) [260]. Harrity and coworkers also described the application of 2-substituted 1-alkynylboronic esters in the Dötz cycloaddition of Fisher chromium carbene complexes, affording in a highly regioselective manner a novel class of hydroxy-naphthyl boron pinacolates (entry 22, Table 1.3) [261]. These reaction products also provided, upon treatment with ceric ammonium nitrate, the corresponding quinone boronic esters. A one-pot 3-component ruthenium-catalyzed process between alkynylboronates, propargylic alcohols, and terminal alkynes provides benzoboroxoles similar to **8** [262], whereas a recent cobalt-catalyzed formal [4+2] cycloaddition leads to arylboronates after an elimination or a chemoselective oxidative treatment that leaves the C–B bond intact (entry 23, Table 1.3) [263].

1.3.1.6 Other Methods

An intriguing deaminoborylation of aniline was recently reported using benzoyl peroxide [264]. This process can provide simple, monofunctionalized arylboron pinacolates in variable yields (entry 24, Table 1.3).

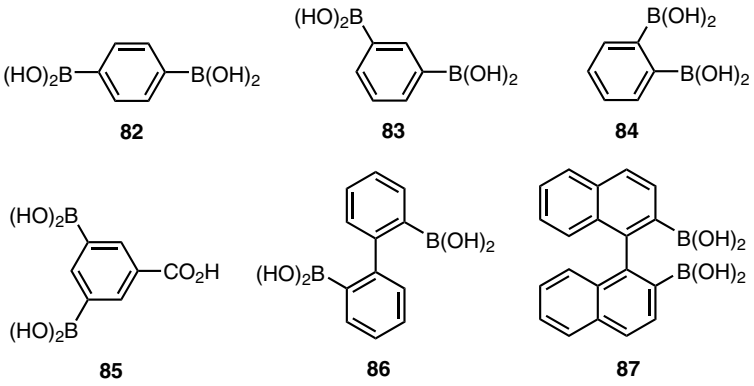


Figure 1.22 Selected examples of diboronic acids.

1.3.2
Diboronic Acids

The preparation of all three substitution patterns of benzenediboronic acid has been reported (Figure 1.22). Although the preparation of the 1,4- and 1,3-benzenediboronic acids **82** and **83** from the corresponding dibromides was well described [186a,265], the preparation of the *ortho*-isomer **84** is more tedious [79, 266]. A number of other mono- and polycyclic aromatic diboronic acids such as **85** [177], **86** [267], and the binaphthyl derivative **87** [268] were described. Tetraboronic acid **6** (Figure 1.2) is a popular building block in materials chemistry (see Chapter 14).

1.3.3
Heterocyclic Boronic Acids

Heterocyclic aromatic boronic acids, in particular pyridinyl, pyrrolyl, indolyl, thienyl, and furyl derivatives, are popular cross-coupling intermediates in natural product synthesis and medicinal chemistry. The synthesis of heterocyclic boronic acids has been reviewed in 2004 [269]. In general, these compounds can be synthesized using methods similar to those described in the above section for arylboronic acids. Of particular note, all three isomers of pyridineboronic acid have been described, including protected forms of the unstable and hitherto elusive 2-substituted isomer, notorious for its tendency to protodeboronate [41, 270]. Many 2-boronyl heteroarenes are sensitive, but they can be stabilized significantly as MIDA adducts (Section 1.2.3.3) [41]. Improvements and variants of the established methods for synthesizing heterocyclic boronic acids have been constantly reported [12, 209]. For example, a Hg–B transmetalation procedure was employed to synthesize a highly functionalized indolylboronic acid (entry 25, Table 1.3) [216]. Recent advances in the preparation of nitrogen-containing heteroaromatic boronic acids and esters include various thermal and catalyzed cycloadditions of alkynylboronates [271] (entry 26).

1.3.4 Alkenylboronic Acids

Alkenylboronic acids constitute another class of highly useful synthetic intermediates. They are particularly popular as partners in the Suzuki–Miyaura cross-coupling reaction for the synthesis of dienes and other unsaturated units present in a large number of natural products (see Section 1.5.3.1). Several methods are available for the preparation of a wide range of alkenylboronic acids with different substitution patterns. These approaches are summarized in a generic way in Figure 1.23 and are described in the following sections.

1.3.4.1 Electrophilic Trapping of Alkenylmetal Intermediates with Borates

Alkenylboronic acids can be synthesized from reactive alkenylmetal species in a way similar to that described above for arylboronic acids (Section 1.3.1.1.1) [272]. Typically, alkenyl bromides or iodides are treated sequentially with *n*-Buli and a borate (entry 1, Table 1.4). A nonpolar trienylboronic acid was synthesized using this approach [274]. As described in Section 1.2.2.2, small boronic acids tend to be highly soluble in water and may be difficult to isolate when made using the traditional approach involving an aqueous workup. In such cases, exemplified with the polymerization-prone ethyleneboronic acid prepared from vinylmagnesium bromide, it has proved more convenient to rather isolate it as a dibutyl ester by extraction of the acidic aqueous phase with butanol [275]. Alkoxy-functionalized butadienyl- and styrenylboronic esters were synthesized from α,β-unsaturated acetals by treatment with Schlosser's base and subsequent trapping with triisopropylborate (entry 2) [276]. Both alkenyl- [277] and cycloalkenylboronates [278] can be made from ketones using a Shapiro reaction with trapping of the alkenyllithium intermediate with a borate (entry 3). Terminal 2-alkenylboronates (α-vinylboronates) are not easily accessible, but a regioselective Ni-catalyzed approach to alkenylalanes followed by borate trapping was recently reported (entry 4) [279].

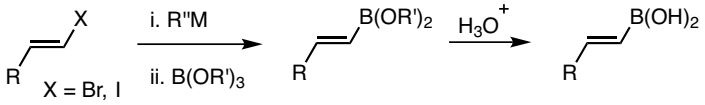
1.3.4.2 Transmetalation Methods

The treatment of trialkylsilyl derivatives with boron halides described in Section 1.3.1.2 is applicable to alkenyltrimethylsilanes [280]. It was employed as a method for preparing ethylene boronic esters [281]. Recently, isomerically pure tetrasubstituted alkenylboronic esters were synthesized by this approach, following an esterification of the intermediate dichloroborane with pinacol (entry 5, Table 1.4) [282]. *trans*-Alkenylboronic acids can also be synthesized from zirconocene intermediates obtained from the hydrozirconation of terminal alkynes (entry 6) [283].

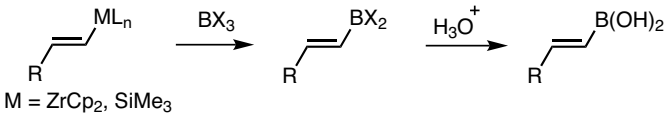
1.3.4.3 Transition Metal-Catalyzed Coupling between Alkenyl Halides/Triflates and Diboronyl Reagents

Alkenyl halides and triflates are suitable substrates in the palladium-catalyzed borylation reaction described for aromatic substrates in Section 1.3.1.3. In this reaction, the geometry of the starting alkenyl halide is preserved in the product, and several functionalities are tolerated in the substrate. At the outset, however, Miyaura

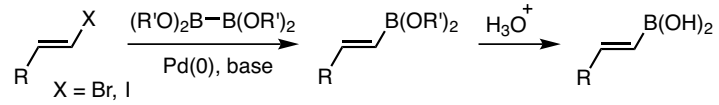
1.3.4.1 Electrophilic trapping of alkenylmetal intermediates with borates



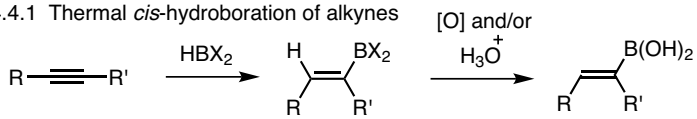
1.3.4.2 Transmetalation methods



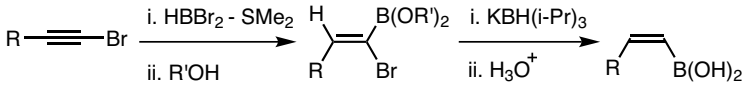
1.3.4.3 Transition metal-catalyzed coupling between ArX/OTf and diboronyl reagents



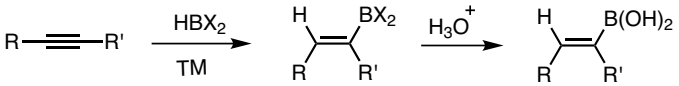
1.3.4.4.1 Thermal *cis*-hydroboration of alkynes



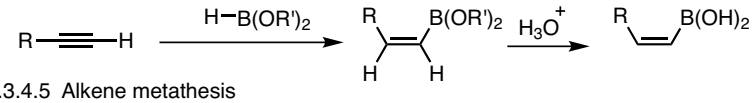
1.3.4.4.2 Indirect *trans*-hydroboration using alkynyl bromides



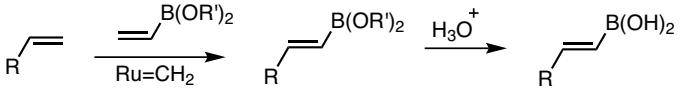
1.3.4.4.3 Transition metal-catalyzed *cis*-hydroboration of alkynes



1.3.4.4.4 Rhodium-and iridium-catalyzed *trans*-hydroboration of alkynes



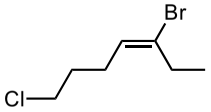
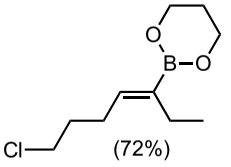
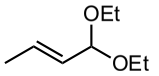
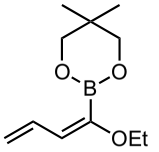
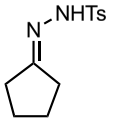
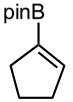
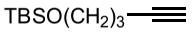
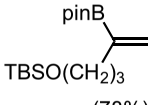
1.3.4.5 Alkene metathesis



1.3.4.6 Diboronylation and silaboration of unsaturated compounds

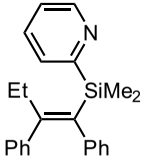
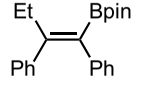
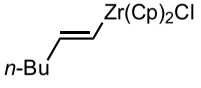
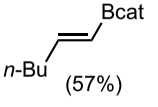
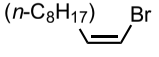
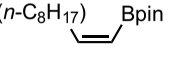
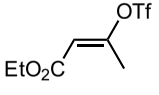
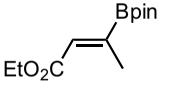
Figure 1.23 Common methods for the synthesis of alkenylboronic acids (esters).

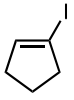
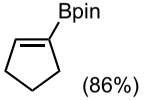
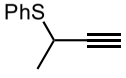
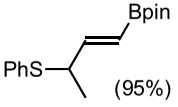
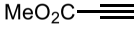
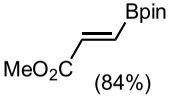
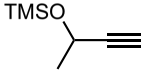
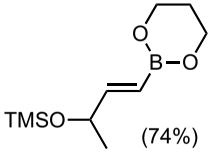
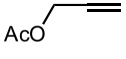
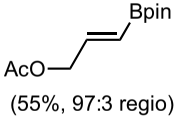
Table 1.4 Selected examples of preparative methods for alkenylboronic acids and esters.

Entry	Substrate	Conditions	Product	Reference
1		i. *s*-BuLi, THF, −78 °C ii. $B(OR')_3$, −78 °C, 1 h iii. HCl/Et_2O, −78 °C to rt iv. H_2O v. $HO(CH_2)_3OH$	 (72%)	[273]
2		i. *n*-BuLi/KO-*t*-Bu (2.5 equiv) THF, −95 °C, 2 h ii. $B(O\text{-}i\text{-}Pr)_3$ (2 equiv) −95 °C to rt iii. H_2O, extraction iv. $HOCH_2CMe_2CH_2OH$ toluene, rt, 12 h	 (93%)	[276]
3		i. *n*-BuLi (4 equiv) TMEDA, hexane −78 °C, 1 h; rt, 2 h ii. *i*-PrOBpin, −78 °C to rt	 (80%)	[278]
4	 (1.1 equiv)	i. DIBALH (1.3 equiv) $Ni(dppp)Cl_2$ (3 mol%) THF, 0 °C, 2 h ii. MeOBpin (3 equiv) 0–80 °C, 24 h	 (78%)	[279]

(*Continued*)

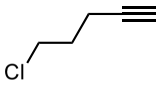
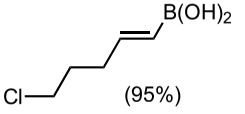
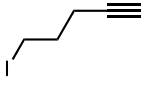
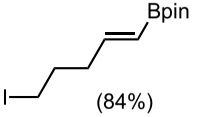
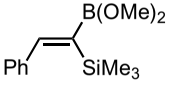
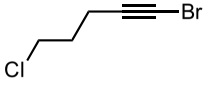
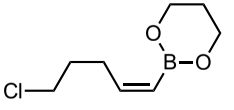
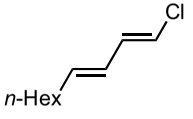
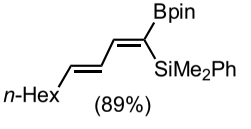
Table 1.4 *(Continued)*

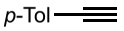
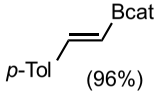
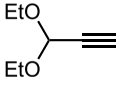
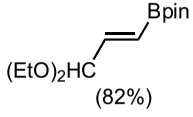
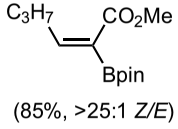
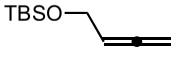
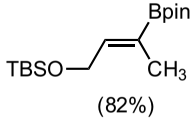
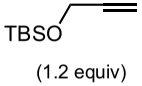
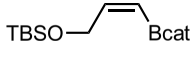
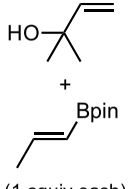
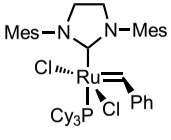
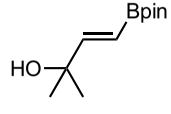
Entry	Substrate	Conditions	Product	Reference
5		1. BCl_3 (2.2 equiv) CH_2Cl_2, −40 °C, 5 h 2. Pinacol, Et_3N	 (82%, *Z*/*E* 98:2))	[282]
6		catBCl CH_2Cl_2, 0 °C	 (57%)	[283]
7		B_2pin_2 (1.1 equiv) $PdCl_2$(dppf) (3 mol%) PPh_3 (6 mol%) KOPh (1.5 equiv) toluene, 50 °C, 5 h	 (74%)	[285]
8		B_2pin_2 (1.1 equiv) $PdCl_2(PPh_3)_2$ (3 mol%) PPh_3 (6 mol%) KOPh (1.5 equiv) toluene, 50 °C, 1 h	 (93%, >99% Z:E)	[286]

9		HBpin (1.5 equiv) $PdCl_2$(dppf) (3 mol%) $AsPh_3$ (12 mol%) Et_3N (3 equiv) dioxane, 80 °C, 16 h		[287]
10		i. Cy_2BH (1 equiv) DME, rt, 1 h ii. Me_3NO (2 equiv), reflux iii. $HOCMe_2CMe_2OH$ rt, 12 h		[295]
11		i. Ipc_2BH, THF −35 °C to 0 °C ii. CH_3CHO (10 equiv) 0–40 °C iii. $HOCMe_2CMe_2OH$ (1 equiv) rt, 12 h		[297,299]
12		i. Ipc_2BH, THF −35 °C to rt, 5 h ii. CH_3CHO (xs) 0 °C; reflux, 12 h iii. $HO(CH_2)_3OH$		[298]
13		i. **93** (1 equiv) ii. H_2O, rt, 0.5 h iii. aq CH_2O (1 equiv) rt, 1 h iv. $HOCMe_2CMe_2OH$ (1.1. equiv) rt, 12 h		[300]

(*Continued*)

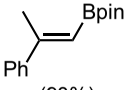
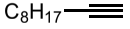
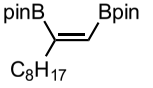
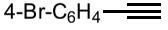
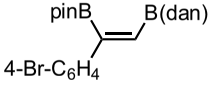
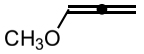
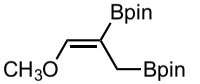
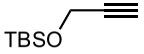
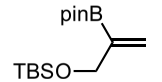
Table 1.4 *(Continued)*

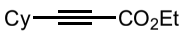
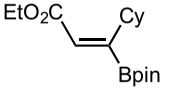
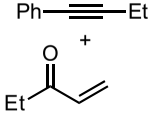
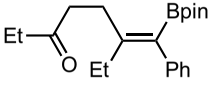
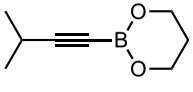
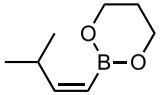
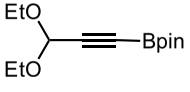
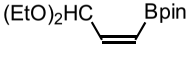
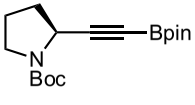
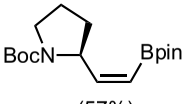
Entry	Substrate	Conditions	Product	Reference
14		i. CBH **57** (1 equiv), 70 °C, 1 h ii. H_2O, 25 °C, 1 h iii. Filtration	 (95%)	[301b]
15		HBpin (2 equiv) CH_2Cl_2, 25 °C, 6 h	 (84%)	[159]
16		i. $HBCl_2$ (1 equiv) BCl_3 (1 equiv), pentane −78 °C; rt, 12 h ii. MeOH, Et_3N, 0 °C	 (46%)	[305]
17		i. $HBBr_2$-SMe_2, CH_2Cl_2 ii. MeOH, pentane iii. K(*i*-PrO)$_3$BH, Et_2O 0 °C to rt, 0.5 h iv. H_2O, 0 °C v. $HO(CH_2)_3OH$	 (89%)	[308]
18		i. *n*-BuLi (1.05 equiv) THF, −90 °C, 15 min ii. $PhMe_2SiB(OCMe_2)_2$ warm up to rt, 12 h	 (89%)	[310]

19		HBcat (1 equiv) $Cp_2Ti(CO)_2$ (4 mol%) C_6H_6, 25 °C, 2 h		[313]
20		HBpin (1.05 equiv) $HZrCp_2Cl$ (5 mol%) CH_2Cl_2, 25 °C, 24 h		[314]
21		pinBH (1.1 equiv) $[(Ph_3P)CuH]$ (2 mol%) Ph_3P (3 mol%)		[319]
22		HBpin (1.5 equiv) $Pt(dba)_2$ (3 mol%) $P(t\text{-}Bu)_3$ (6 mol%) toluene, 50 °C, 2 h		[321]
23		HBcat (1 equiv) $[Rh(cod)Cl]_2$ (1.5 mol%) PPr_3 (6 mol%) Et_3N (1 equiv) cyclohexane, rt, 2 h		[322]
24				[327]

(*Continued*)

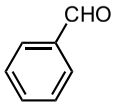
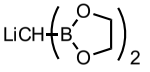
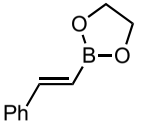
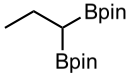
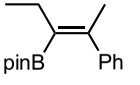
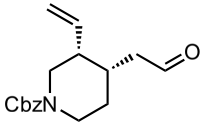
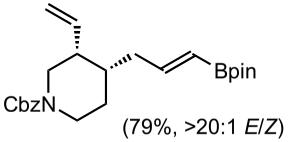
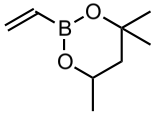
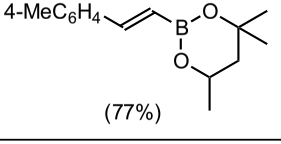
Table 1.4 *(Continued)*

Entry	Substrate	Conditions	Product	Reference
25		B_2pin_2 (0.67 equiv) $[RhCl(CO)(PPh_3)_2]$ (5 mol%) 3 : 1 toluene–CH_3CN 80 °C, 3 d	 (90%)	[331]
26	 (1.1 equiv)	B_2pin_2 (1 equiv) $Pt(PPh_3)_4$ (3 mol%) DMF, 80 °C, 24 h	 (86%)	[332]
27		(dan)BBpin **64** (0.67 equiv) $[IrCl(COD)]_2$ (1.5 mol%) toluene, 80 °C, 24 h	 (83% 98:2 *E/Z*)	[165]
28	 (1.5 equiv)	B_2pin_2 (1 equiv) $Pt(dba)_2$ (10 mol%) PCy_3 (10 mol%) toluene, 50 °C, 18 h	 (85%)	[334]
29		B_2pin_2 (1.1 equiv) CuCl (1.1 equiv) KOAc (1.1 equiv) $P(t\text{-}Bu)_3$ (1.1 equiv) DMF, rt, 16 h	 (62%, 91:9 regioselectivity)	[335]

30		B_2pin_2 (1.1 equiv) CuCl (3 mol%) NaO-*t*-Bu (6 mol%) Xantphos (3 mol%) MeOH (2 equiv) THF, rt	 (99%)	[336]
31		B_2pin_2 (1.5 equiv) $[Ni(COD)_2]$ (5 mol%) *n*-Bu_3P (10 mol%) tol/MeOH 3 : 1 40 °C, 10 h	 (80%)	[339]
32		i. H_2, Lindlar, pyridine 1,4-dioxane, rt, 1.5 h ii. H_2O iii. $HO(CH_2)_3OH$, pentane	 (83%, 95% *Z*)	[341]
33		i. $HZrCp_2Cl$ (1.2 equiv) THF, 25 °C, 0.5 h ii. H_2O, 0.5 h	 (82%)	[342]
34		i. Cy_2BH (1.0 equiv) Et_2O, 0 °C ii. AcOH (2.2 equiv), 0 °C iii. $HOCH_2CH_2NH_2$, 0 °C to rt	 (57%)	[343]

(*Continued*)

Table 1.4 *(Continued)*

Entry	Substrate	Conditions	Product	Reference
35		 THF/CH_2Cl_2 –78 °C, 3 h	 (87%, >93% *E*)	[348]
36		i. LTMP THF, 0 °C, 5 min ii. MeCOPh	 (94%, >99:1)	[352]
37		$Cl_2CHBpin$ (2 equiv) C_rCl_2 (8 equiv) LiI (4 equiv) THF, 25 °C	 (79%, >20:1 *E*/*Z*)	[354]
38		4-MeC_6H_4I $Pd(OAc)_2$ (5 mol%) PPh_3 (12 mol%) nBu_3N (1.2 eq) toluene, reflux, 8 h	 (77%)	[355]

and coworkers found that the conditions utilized for aryl halide substrates led to low yields of the desired alkenylboronate due to competing reactions such as the formation of homocoupled product of Suzuki cross-coupling [284]. To improve the rate of transmetalation between the diboronyl reagent (B_2Pin_2) and the oxidative addition Pd(II) intermediate, stronger bases were evaluated. In the optimal procedure, potassium phenoxide was found to be the most effective base, with a less polar solvent (toluene) than that used with aryl halides, and triphenylphosphine as ligand in place of dppf. Alkenyl bromides and triflates were found to be superior over iodides, and generally afforded good yields in the 70–90% range. The mildness of these conditions opened up a rather impressive scope of suitable substrates [285], including *Z*-alkenes (entry 7, Table 1.4), and both acyclic and cyclic ones with functionalities such as alkyl halides, silyl-protected alcohols, and carboxylic esters (entry 8) [286]. Pinacolborane was found to be effective in the borylation of alkenyl halides under a new set of optimal conditions (entry 9) [287]. No competing hydroboration was observed, but acyclic *Z*-configured substrates are inverted under these reaction conditions. Likewise, borylation of alkenyltriflates within a pyran ring can lead to isomerization to the corresponding allylboronate [287].

1.3.4.4 **Hydroboration of Alkynes**

1.3.4.4.1 **Thermal cis-Hydroboration** Since its discovery by Brown and Rao in 1956 [288], hydroboration chemistry has been a central reaction in the preparation of organoboron compounds [289]. The *cis*-hydroboration of terminal alkynes provides ready access to *trans*-2-substituted alkenylboronic acids [290], and several borane reagents have been used for this purpose (Figure 1.24). Unsymmetrical internal alkynes usually give mixtures of regioisomeric alkenylboron compounds. With terminal alkynes, however, the hydroboration is highly regioselective and adds boron at the terminal carbon. Likewise, whereas small borane reagents tend to undergo a double hydroboration with alkyne substrates, more hindered boranes allow the hydroboration process to stop with ease after one addition, avoiding further hydroboration of the desired product into a diboroalkane [290]. Thus, the bulky dialkylborane reagents disiamylborane (**88**) [289], thexylborane (**89**) [291], dicyclohexylborane (**90**) [292], and 9-BBN (**91**) [293] all react with terminal alkynes to provide

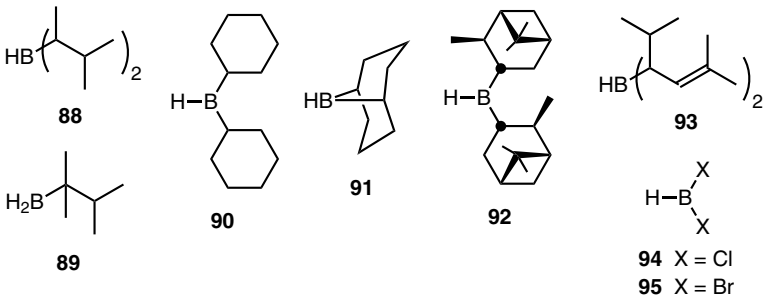


Figure 1.24 Common hydroborating agents for alkynes.

2-substituted dialkylalkenylboranes in a very high regioselectivity. The corresponding alkenylboronic acid may be obtained after an appropriate oxidative workup, which is generally performed with a mild and selective oxidant for the two sp^3 C–B bonds. Toward this end, trimethylamine oxide was found most suitable [294], leaving not only the alkenyl boron–carbon bond intact but also a selenide and a sulfide substituent (entry 10, Table 1.4) [295]. In the hydrolysis of the resulting alkenylboronate, the ensuing separation of the desired boronic acid from the alcohol by-product originating from the oxidation of the dialkylborane is not always straightforward. Hoffmann and Dresely described a procedure with dicyclohexylborane where the boronic acid is esterified *in situ* as a pinacolate after the oxidation step and then purified by distillation to eliminate the residual cyclohexanol [295]. This way, several functionalized (*E*)-1-alkenylboronates were isolated, and it was found that the use of DME, a polar coordinating solvent, was essential when using a propargylic ether as substrate. For substrates that may be sensitive to the oxidative workup or to avoid the cyclohexanol by-product, diisopinocampheylborane (**92**, Figure 1.24) [296] offers a milder alternative. With this reagent, the alkyne is hydroborated and then subjected to a gentle oxidative dealkylation using acetaldehyde to afford a diethyl alkenylboronic ester along with 2 equiv of pinene [297–299]. The crude diethyl alkenylboronate can be transesterified with diols such as pinacol to yield the corresponding pinacol ester, which in most cases must be purified by distillation or chromatography. Although the synthesis of several highly functionalized alkenylboronates was reported using this method (entries 11 and 12), it is often difficult to completely eliminate the pinene by-product by distillation. The newer reagent di(isopropylprenyl)borane, **93**, was described [300]. Much like reagent **92**, it features a mild neutral workup with aqueous formaldehyde or water (entry 13).

The use of 4,4,6-trimethyl-1,3,2-dioxaborinane (**56**, Figure 1.15) [157], catecholborane (**57**) [301], pinacolborane (**58**) [159], or the more reactive 1,3,2-dithiaborolane (**59**) [161] provides the boronic acid derivative directly after a nonoxidative hydrolytic workup. Yet, these methods are not without disadvantages. Dialkoxyboranes are less reactive than the dialkylboranes described above. For example, alkyne hydroborations with catecholborane are often performed at temperatures as high as 100 °C, whereas dialkylboranes such as Cy_2BH were found to catalyze these hydroborations at ambient temperature [302]. Although catecholborane was employed with highly functionalized substrates [303], it was reported that it does not tolerate acetal or ether functionalities at the propargylic carbon [295, 298], and the acidic catechol released in the aqueous workup needs to be neutralized and removed from the mixture (entry 14). By producing the robust pinacolate ester in a single operation, the use of pinacolborane (**58**) is quite advantageous, although the addition also tends to be sluggish (entry 15). Dibromoborane (**95**, Figure 1.24), in the form of a methyl sulfide complex, conveniently gives access to 1-alkenylboronic acids bearing alkyl or aryl substituents at the 2-position following alcoholysis of the intermediate alkenyldibromoborane [304]. Several other functionalities, however, are not well tolerated by this reagent. The related dichloroborane (**94**) was found to undergo a regioselective hydroboration with silylacetylenes, giving the (*E*)-1-trimethylsilyl-1-alkenylboronic ester after methanolysis (entry 16) [305]. Dichloroborane is difficult to

handle, but a simple variant presumed to generate it *in situ* by reaction of trimethylsilane with boron trichloride was also shown to hydroborate alkynes [306]. Alternatively, a more recent report demonstrated the suitability of the stable and commercially available Cl_2BH–dioxane complex for the preparation of 1-alkenylboronic acids [307].

1.3.4.4.2 **Indirect trans-Hydroboration Using Alkynyl Bromides** All the above hydroboration methods provide terminal *trans*-alkenylboronic acids by a highly regioselective *syn*-addition of the B–H bond across the terminal alkyne. To provide the *cis*-alkenylboronic acids, Brown and Imai developed an ingenious two-step method based on the regioselective hydroboration of bromoalkynes with dibromoborane (Figure 1.23) [308]. In this procedure, the resulting (*Z*)-1-bromo-alkenyldibromoboranes are transformed into the corresponding esters through simple alcoholysis. The isolated boronates are then treated with potassium triisopropoxyborohydride (KIPBH) to effect a stereospecific bromide substitution by inversion of configuration, thereby affording the *cis*-alkenylboronic esters. Although dibromoborane presents a limited scope of chemoselectivity, KIPBH is relatively mild. For example, it tolerates a primary alkyl chloride on the substrate (entry 17, Table 1.4). Furthermore, an extension of this approach employing organolithium or Grignard reagents in place of KIPBH leads to the stereoselective preparation of (*E*)-1-substituted-1-alkenylboronic esters that could not be obtained via the hydroboration of alkynes [309]. Recently, a similar nucleophilic substitution mechanism has also been proposed in a new method involving the addition of alkenyllithium intermediates to the diboronyl reagent B_2pin_2 or the related dimethylphenylsilyl(pinacolato)borane [310]. In this reaction, which accomplishes a geminal difunctionalization of formal alkenylidene-type carbenoids, 1,1-diboronylalkenes or 1-silyl-1-alkenylboronates are produced (entry 18).

1.3.4.4.3 **Transition Metal-Catalyzed cis-Hydroboration** Since the discovery of the rhodium-catalyzed hydroboration of alkenes by Männig and Nöth in 1985 [311], the application of this method to alkynes has generally not provided satisfactory results [312]. He and Hartwig, however, found that dicarbonyltitanocene effectively catalyzes the hydroboration of alkynes with catecholborane without the contamination of by-products of catecholborane decomposition usually observed under rhodium catalysis (entry 19, Table 1.4) [313]. By taking advantage of the superior stability of pinacolborane over catecholborane, Pereira and Srebnik developed a very convenient zirconocene-catalyzed procedure for the pinacolboration of terminal alkynes (entry 20) [314]. This method, which features lower reaction temperature and times compared to the noncatalyzed variant of Knochel and coworkers [159], provides the (*E*)-1-alkenylboronates as their convenient pinacolate ester in high yields and high regioselectivity. A modified procedure affords improved *E*/*Z* selectivities with oxygen-containing alkynes [315], and the efficient use of reagent **56** was also reported [316]. Other transition metal catalysts such as $Rh(CO)(Ph_3P)_2Cl$ and $NiCp(Ph_3P)Cl$ were also found to be effective in conjunction with pinacolborane as the hydroboration agent [317]. Like the noncatalyzed hydroboration, internal

alkynes tend to give mixtures of regioisomers. Using thioalkynes, however, a nickel-catalyzed catecholboration method provides 2-alkylthio-1-alkenylboronates in a high regioselectivity [318]. A copper hydride-catalyzed copper–to–boron transmetalation procedure with pinacolborane affords 1-carboalkoxy alkenylboronates regioselectively (entry 21) [319].

A $Pd(PPh_3)_4$-catalyzed catecholboration of an enyne afforded an allenylboronate [320]. Miyaura and coworkers also reported the $Pt(dba)_2$-catalyzed pinacolboration of terminal allenes, and the regioselectivity was found to be highly dependent on the nature of the added phosphine ligand [321]. For example, whereas the bulky tris(2,4,6-trimethoxyphenyl)phosphine often led to substantial amounts of the external Markovnikov product, the use of tris(*t*-butylphosphine) provided the internal hydroboration product as single isomer (entry 22, Table 1.4). It is noteworthy that the resulting 1-substituted-1-alkenylboronate is not accessible regioselectively using the uncatalyzed hydroboration of terminal allenes or terminal alkynes.

1.3.4.4.4 **Rhodium- and Iridium-Catalyzed trans-Hydroboration** Direct alkyne hydroboration methods, whether catalyzed or not, afford *trans*-alkenylboronic acids by a highly regioselective *syn*-addition of the reagent's B−H bond across the terminal alkyne. The indirect Brown method to effect formal *trans*-hydroboration (Section 1.3.4.4.2) is limited by the need for a bromoalkyne and the harshness of the dibromoborane reagent employed. To fill this important methodological void and allow a direct and mild formation of *cis*-alkenylboronic acids, a true "*trans*-hydroboration" method was developed by Miyaura and coworkers. It was found that the hydroboration of alkynes with either catecholborane or pinacolborane in the presence of triethylamine and catalytic amounts of rhodium or iridium phosphine complex provides good to high yields of (*Z*)-1-alkenylboronic esters in a very high selectivity (entry 23, Table 1.4) [322]. Interestingly, deuterium labeling experiments showed that the *cis*-hydrogen substituent does not originate from the borane, it comes from the terminal alkyne instead. Based on this information, a mechanism involving migration of the acetylenic hydrogen and proceeding through a metal–vinylidene complex was proposed [322] to explain the selectivity of this unique "*trans*-hydroboration" method that has been employed in complex natural product synthesis [323].

1.3.4.5 Alkene Metathesis

Recently, the advent of efficient catalysts for alkene metathesis has opened up new opportunities for the synthesis of alkenylboronic acids. For example, it was shown that ring-closing metathesis of dienylboronic acids provides cyclic alkenylboronic acids that would be difficult to obtain otherwise [324]. Chemoselectivity in cross-metathesis chemistry is a significant issue that tends to pose strict limits to the synthesis of acyclic alkenes using these novel catalysts [325]. With most terminal alkenes, mixtures of disubstituted alkene products are obtained, and often with a low *E*/*Z* selectivity. Exceptionally, a number of alkene substrates are prone to undergo a highly chemoselective cross-metathesis with other terminal alkenes [325]. Fortunately, ethylene and 1-propenyl pinacol boronic esters rank among those favorable partners [326, 327]. Morrill and Grubbs discovered that they undergo

a clean cross-metathesis with terminal alkenes, catalyzed by a ruthenium alkylidene, to provide the (*E*)-1-alkenylboronic ester in high selectivity (entry 24, Table 1.4) [327]. This methodology was tested in the synthesis of complex molecules such as epothilone analogues [328]. Ene–yne metathesis reactions based on alkynylboronic ester annulation strategies provide polysubstituted 2-butadienyl boronic esters [329, 330].

1.3.4.6 Diboronylation and Silaboration of Unsaturated Compounds

Diboronyl reagents such as B_2pin_2 (**63**) can be employed in various ways to access mono- or diboronyl alkenes depending on the reaction conditions [249]. Marder and coworkers developed a dehydrogenative borylation of vinylarenes to access 2,2-disubstituted-1-alkenylboronates that are not accessible by standard alkyne hydroboration chemistry [331]. By using the catalyst precursor $RhCl(CO)(PPh_3)_2$ and B_2pin_2 or B_2neop_2, the authors found conditions that prevent any significant competitive hydrogenation or hydroboration of the product. For example, (*E*)-Ph(Me)C=CH(Bpin) was obtained from α-methylstyrene in high yield and high geometrical selectivity (entry 25, Table 1.4). A mechanism that accounts for the beneficial role of acetonitrile as cosolvent was proposed. Diboronyl compounds add onto terminal and internal alkynes under platinum catalysis to provide *cis*-1,2-diboronylalkenes [332]. For example, $Pt(PPh_3)_4$ catalyzes the addition of bis(pinacolato)diboron (**63**) to 1-decyne, affording the corresponding alkenylbisboronate (entry 26, Table 1.4). Several other metal complexes tested, including palladium, rhodium and nickel complexes failed to promote the same reaction. Recently, the use of reagent **64** (Figure 1.16) was found to give high selectivities for the Bpin group on the internal position (entry 27) [165]. Mechanistically, these reactions' catalytic cycle is thought to be initiated by the oxidative addition of Pt(0) into the B−B bond, followed by a *cis*-boro-platination of the alkyne, and the cycle is terminated by the reductive elimination of the alkenyl-Pt(II)-Bpin unit to regenerate the Pt(O) catalyst [333]. Allenes also react similarly (entry 28) [334]. In a related process, B_2pin_2 was found to add to terminal alkynes at room temperature in the presence of stoichiometric copper (I) chloride and potassium acetate as the base [335]. It was proposed that a boron–copper transmetalation is involved, giving a putative boryl-copper species (CuBpin). The reaction provides a variable ratio of 1-boronyl and 2-boronyl alkenes depending on the additive employed, which can either be a phosphine or LiCl (entry 29). With α,β-ethylenic esters, *Z*-configured β-boronyl enoates are obtained [336] (entry 30), thus complementing the above formal hydroboration approach [299]. Murakami and coworkers reported a palladium-catalyzed silaboronation of allenes, affording 2-boronyl-allylsilanes [337]. The same group also described a palladium- and nickel-catalyzed intramolecular cyanoboronation of homopropargylic alkynes [338]. An interesting nickel-catalyzed borylative coupling of alkynes and enones provides tri- and tetrasubstituted alkenylboronates (entry 31) [339]. Many more diboronylation and silaboration processes have been developed and are described in detail in Chapter 3. It should be noted that unlike the direct aromatic borylations discussed in Section 1.3.1.4, direct transition metal-catalyzed borylations of alkenes' C−H bonds with diboronyl reagents are complicated by competitive allylic borylation [340].

1.3.4.7 Other Methods

The conceptually simple, photochemical *E*–*Z* isomerization of double bonds is not an efficient approach for accessing geometrically pure alkenylboronic esters [305, 309b]. Alkynylboronic esters, however, are very useful precursors of alkenylboronates. For instance, they can be selectively hydrogenated over Lindlar's catalyst with 1,4-dioxane as the optimal solvent for providing (*Z*)-1-alkenylboronates with stereochemical purity over 95% (entry 32, Table 1.4) [341]. Likewise, highly pure (*Z*)-1-alkenylboron pinacolates were isolated from the corresponding alkynylboronates and from a sequence of regioselective hydrozirconation and aqueous protonolysis (entry 33) [342]. A similar hydroboration/protodeboronation approach was recently reported, giving functionalized (*Z*)-1-alkenylboronates (entry 34) [343]. In the past few years, various transition metal-catalyzed alkylative insertions and cycloadditions of alkynylboronates [344] and allenylboron pinacolate [345] have emerged, affording tri- and tetrasubstituted alkenylboronates usually with limited scope.

Addition of a α-silylallylboronate to aldehydes gives 4-alkoxy (*E*)-1-alkenylboronates [346]. Matteson and Majumdar have reported a Peterson-type olefination of the anion derived from an α-trimethylsilylmethylboronic ester ($LiCH(SiMe_3)Bpin$) [347]. Addition of the latter onto aldehydes provided the corresponding alkenylboronic ester as a mixture of geometrical isomers (~70 : 30 *Z*/*E*). No further optimization was reported toward controlling the *E*/*Z* selectivity in this potentially useful and unique method for synthesizing alkenylboronic esters from aldehydes. The corresponding lithiomethylenediboronic esters tend to provide mixtures favoring the *E*-isomer (entry 35) [348, 349], and this approach to access alkenylboronic acids from aldehydes was employed in the total syntheses of natural products such as palytoxin [350] and the macrolide antibiotic rutamycin B [351]. An extension of this method using lithium 2,2,6,6-tetramethylpiperazide (LTMP) as base and ketones as electrophiles produces tetrasubstituted alkenylboronates (entry 36) [352]. A variant of the traditional Takai reaction using $Cl_2CHBpin$ provides *trans*-1-alkenylboronic esters from aldehydes [353], and this procedure was recently employed in a synthesis of quinine (entry 37) [354]. The pinacol and 2-methyl-2,4-pentanediol esters of ethylene boronic acid are efficient substrates for Heck couplings with aryl and alkenyl halides, giving 2-aryl- and 2-butadienylboronates, respectively, with minimal side product from Suzuki–Miyaura cross-coupling (entry 38) [355]. A radical promoted variant employs xanthates to produce 3-oxo-(*E*)-1-alkenylboronates in low yields [356]. To access 2,2-disubstituted-1-alkenylboranes, a two-step sequence of bromoboration/Negishi coupling was described [357]. Advances in the Pd-catalyzed intramolecular carboboration of alkynes give access to tetrasubstituted alkenylboronates [358]. The synthesis of alkenylboronates using other types of additions and cycloadditions to alkynylboronates is described elsewhere (Chapter 3) [258, 359].

1.3.5 Alkynylboronic Acids

Like their aryl and alkenyl counterparts, alkynylboronic acids can be made by displacement of magnesium or lithium acetylides with borate esters. For example,

Matteson and Peacock described the preparation of dibutyl acetyleneboronate from ethynylmagnesium bromide and methyl borate [360]. It was observed that the C−B linkage is stable in neutral or acidic hydroxylic solvents, but readily hydrolyzes in basic media such as aqueous sodium bicarbonate. Brown and coworkers eventually applied their organolithium procedure toward the preparation of alkynylboronic esters, and in this way provided a fairly general access to this class of compounds [361].

1.3.6 Alkylboronic Acids

Compared to aryl- and alkenylboronic acids, alkylboronic acids and esters have not found widespread use as synthetic intermediates aside for their oxidation into alcohols (Section 1.5.2.1). This is due in part to their limited shelf stability. In addition, their transmetalation with transition metal catalysts such as palladium is presumed to be more difficult compared to unsaturated and aromatic boronic acid derivatives [362]. For example, alkylboronic acids have long been known to be reluctant substrates in the Suzuki–Miyaura cross-coupling reaction, and they have become suitable only very recently with the use of special bases and the advent of new and highly active catalyst systems (Section 1.5.3.1 and Chapter 4). Arguably, the most synthetically useful class of alkylboronic acids are the α-haloalkyl derivatives popularized by Matteson (Section 1.3.8.4). Specifically, the Matteson asymmetric homologation of α-haloalkylboronic esters provides a general access to functionalized, chiral alkylboronic esters in high enantioselectivities. Recent applications of this elegant chemistry and variants thereof are also described in Chapter 10.

Alkylboronic acids and esters can also be synthesized from the trapping of organomagnesium and organolithium intermediates with borates. Methylboronic esters, for example, are made using the condensation of methyllithium and triisopropylborate [207]. Likewise, the useful α-chloromethylboronate reagents **96** (Figure 1.25) can be made with the *in situ* trapping variant whereby butyllithium is added to a mixture of ICH_2Cl and triisopropylborate [363]. The corresponding bromide (**97**) [364] and iodides (**98**) [365] were also reported. Recently, a method for the preparation of benzylic boronates was devised using a catalytic amount of magnesium [366]. Both catalyzed and uncatalyzed hydroboration of alkenes serve as powerful methods to access enantiopure alkylboronic esters. Because a selective oxidation of two of the resulting three B−C bonds following hydroboration with dialkylboranes is difficult, a hydroboration route to alkylboronic acids and esters is limited to reagents such as ipc_2BH (**92**), dihaloboranes, and dialkoxyboranes (e.g., catechol- and pinacolborane). The asymmetric hydroboration of alkenes with ipc_2BH or $ipcBH_2$ (Equation 1.35, Figure 1.25) [367, 368], or using chiral rhodium catalysts [369, 370], constitutes well-established routes to access chiral alkylboronic esters or the corresponding alcohols or amines after a stereospecific oxidation of the B−C bond (Sections 1.5.2.1 and 1.5.2.2). A remarkable NHC-Cu(I)-catalyzed formal hydroboration of aryl-substituted alkenes was recently reported (Equation 1.36) [371]. Chiral cyclopropylboronic esters were obtained by catalytic enantioselective pinacolboration of cyclopropenes (Equation 1.37) [372], and other methods to

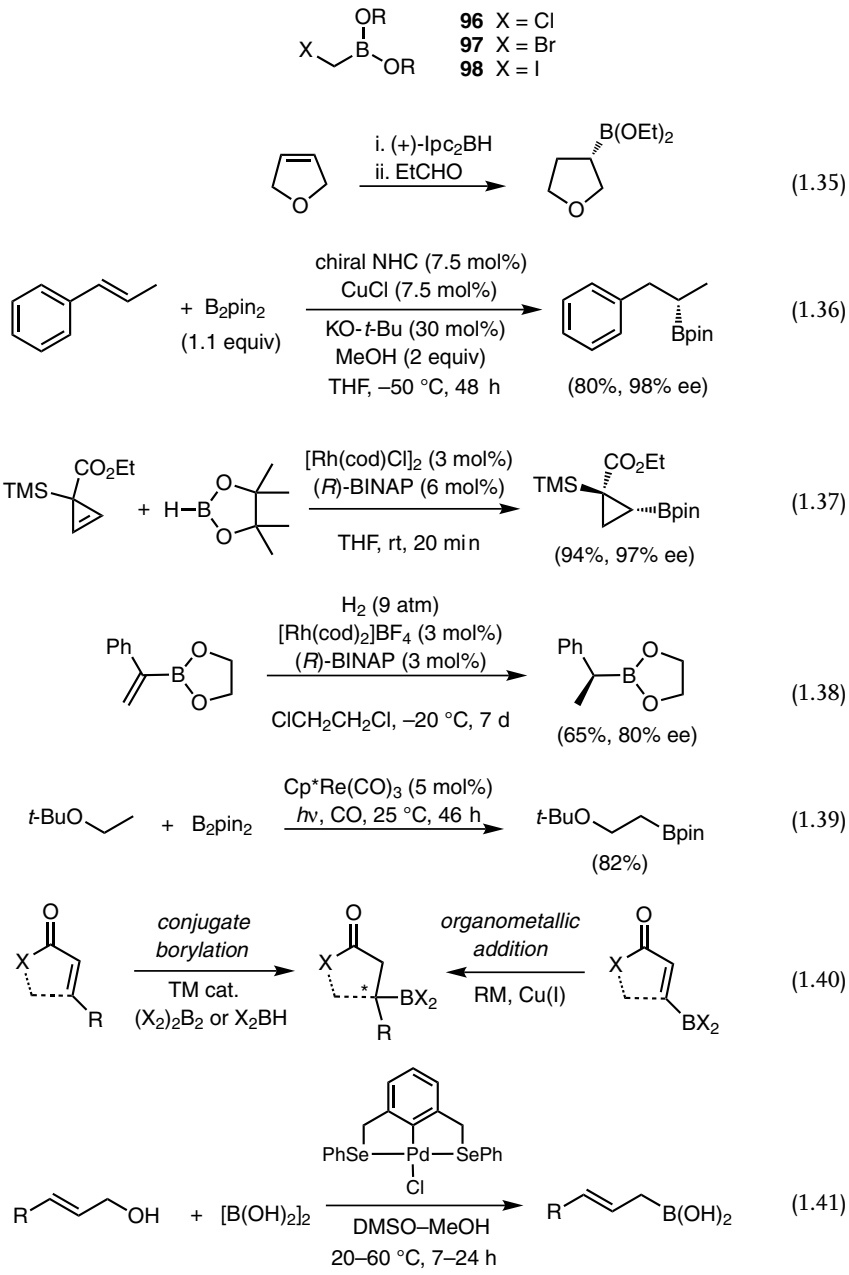


Figure 1.25 Alkylboronic acids (esters): selected examples of enantioselective preparative methods.

access vinylcyclopropylboronic esters are known [373]. Enantiomerically enriched alkylboronic esters can also be obtained through less common methods such as the hydrogenation of chiral alkenylboronic esters [374] and even with enantioselective variants using chiral catalysts (Equation 1.38) [375a]. Though not a general method, alkylboronic acids have also been isolated via a regioselective rhenium-catalyzed C–H activation/boronylation reaction (Equation 1.39) [250b]. Several other transition metal-catalyzed mono- and diboration reactions of aldehydes [376], unactivated alkenes [377], alkynes, [378], and dienes [379] provide new ways to chiral alkylboronic esters. The transition metal-catalyzed asymmetric conjugate borylation of α,β-unsaturated carbonyl compounds [380] delivers alkylboronates with high enantioselectivities (Equation 1.40) [381]. Recently, metal-free, carbene-catalyzed and chiral phosphine-catalyzed variants have appeared [382]. An efficient alternative is the asymmetric conjugate addition to β-boronyl acceptors (Equation 1.40) [383].

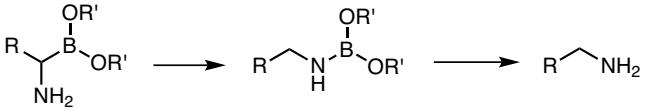
1.3.7
Allylic Boronic Acids

Because of their tremendous utility as carbonyl and imine allylation agents (Section 1.5.3.6 and Chapter 8), several methodologies have been developed for synthesizing allylic boronic acids and their various esters. The preparation and reactions of allylboronic esters have been reviewed in the past 5 years [384], but new methods appear constantly, including asymmetric variants [385]. Among others, metal-catalyzed diborylation of allylic electrophiles, including free alcohols (Equation 1.41) [386], and even direct allylic borylation of alkenes [340] provide mild approaches to allylic boronates. Recently, efficient methods to produce α-substituted allylic boronates using catalytic regio- and stereoselective hydroborations of 1,3-dienes have appeared [387].

1.3.8
Chemoselective Transformations of Compounds Containing a Boronic Acid (Ester) Substituent

New boronic acid derivatives can be made by the derivatization of compounds that already contain a boronic acid (ester) functionality. The scope of possible transformations, however, relies on the compatibility of these reaction conditions with the boronate group and, in particular, on the oxidatively labile C–B bond. One seminal example that best illustrates the limitations imposed by the intrinsic reactivity of boronic acids is that of α-aminoalkylboronic acids, the boron analogues of amino acids (Section 1.3.8.4) [388]. The synthesis of these important derivatives remained an elusive goal for several years. The reason for the instability of compounds of type **99** is the incompatibility of free α-amino groups possessing hydrogen substituents, which undergo a spontaneous 1,3-rearrangement to give the homologated amine **101** following hydrolysis of the transposed intermediate **100** (Equation 1.42) [124]. It was eventually found that this undesired process could be prevented through a rapid acylation of the amino group or its neutralization as a salt [124]. This undesirable

rearrangement was later exploited in a method for mono-*N*-methylation of primary amines [389]. Also of note is the lability of alkylboronic acids with a leaving group in the β-position, which, as exemplified with the formation of ethylene by debromoboronation of 2-bromoethaneboronic acid, are unstable under basic conditions [390]. A review by Matteson provides a detailed overview of the chemical compatibility of boronic acids and esters, and can undoubtedly be of great advice for evading trouble when derivatizing a boronic acid-containing compound [391]. Therefore, only selected examples of boronate-compatible transformations will be discussed in the following sections. It is noteworthy that accrued information on the chemical compatibility of free boronic acids has recently made it possible to perform multistep syntheses on boronic acid-containing compounds. This is realized in conjunction with a new liquid–liquid, pH-driven phase switching strategy employing sorbitol as a phase transfer agent [392]. For example, the antilipidemic drug ezetimibe (**102**) was synthesized in five steps from *p*-boronobenzaldehyde, making use of ubiquitous transformations such as [2 + 2] cycloaddition, cross-metathesis, and hydrogenation without a need for chromatographic purifications of intermediates up until the final productive detagging operation that unmasked the desired phenol via C–B bond oxidation (Figure 1.26) [392].



(1.42)

1.3.8.1 Oxidative Methods

The sensitivity of the B–C bond of boronic acids and esters to oxidation was discussed in Section 1.2.2.5.2. Although basic hydrogen peroxide and other strong oxidants rapidly oxidize B–C bonds, a certain degree of selectivity is possible. For example, sulfide and alcohol functionalities can be selectively oxidized without affecting a pinacol boronate (Equations 1.43 and 1.44, Figure 1.27) [295]. The reagent 2-iodoxybenzoic acid (IBX) oxidizes alcohols selectively on substrates containing a free arylboronic acid moiety [392]. On the other hand, the epoxidation of alkenylboronic esters is known to fail, but it can be achieved indirectly from trifluoroborate salts (Equation 1.32, Figure 1.19) [197]. The permanganate oxidation method is commonly employed to access carboxy-substituted arylboronic acids from methyl-substituted precursors [393]. Radical bromination of methyl-substituted arylboronic acids provides a route to the corresponding hydroxymethyl and formyl derivatives (Equations 1.45 and 1.46) [184]. The bromination of *p*-tolylboronic acid, followed by alkylation of acetaminomalonic ester, hydrolysis, and decarboxylation, affords 4-borono-phenylalanine [184].

1.3.8.2 Reductive Methods

Care must be taken in using strong hydride reagents as they can transform boronic esters into dihydridoboranes (Section 1.2.3.7). A subsequent hydrolysis, however,

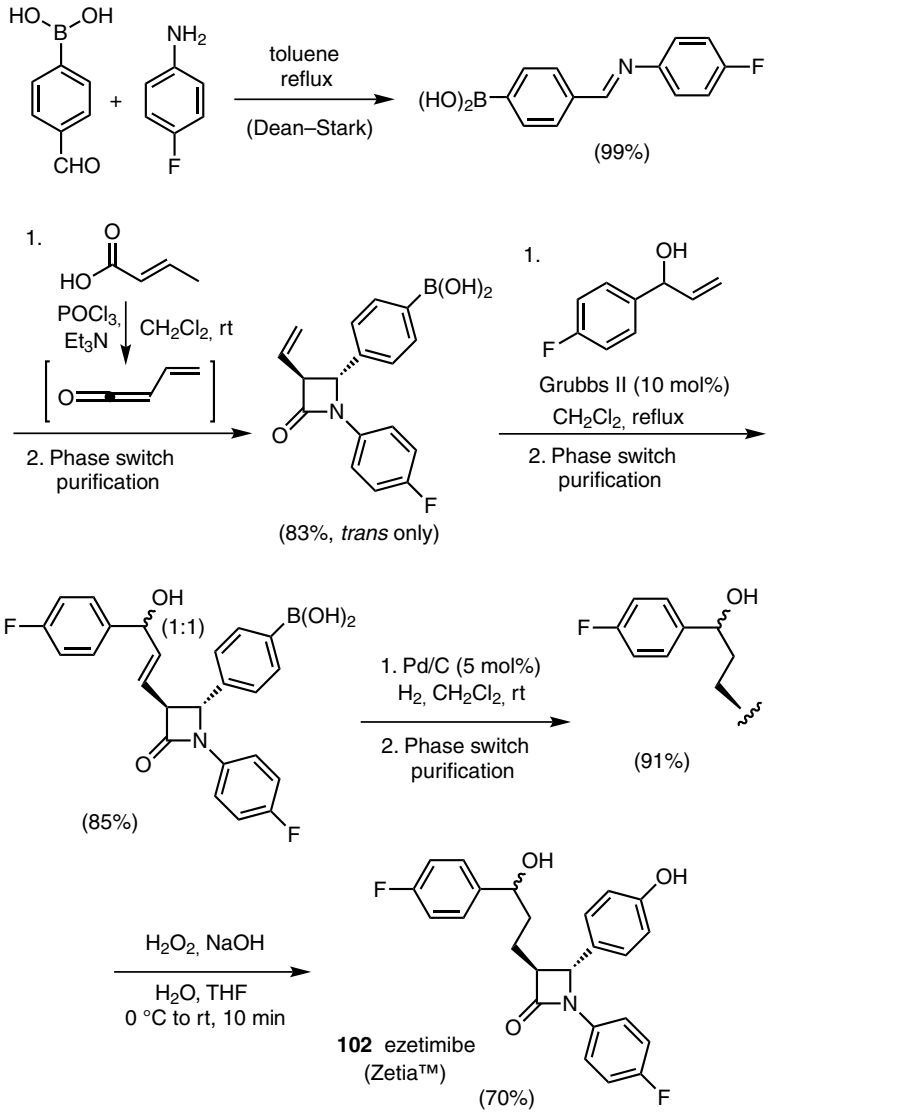
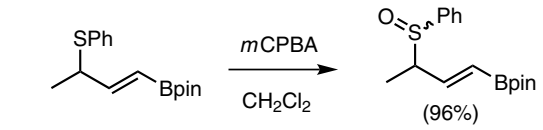


Figure 1.26 Chemoselective, multistep phase switch synthesis of ezetimibe using boronic acid as a phase tag.

can restore the boronic acid. DIBALH reduced a carboxyester selectively on a substrate containing a free arylboronic acid moiety [392]. Catalytic hydrogenation methods appear to be quite compatible with boronate groups and even with free boronic acids, as shown by the examples of Figure 1.26 and Figure 1.28 (Equations 1.47 and 1.48) [394, 395].



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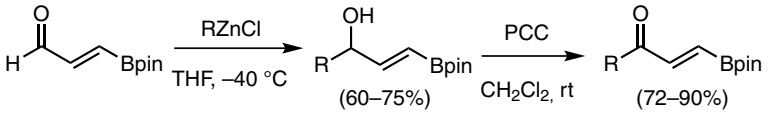

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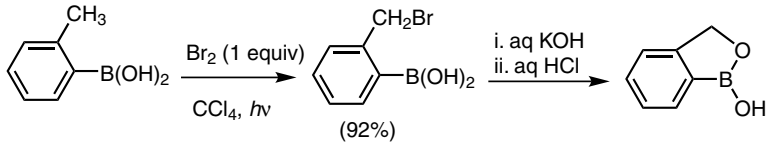

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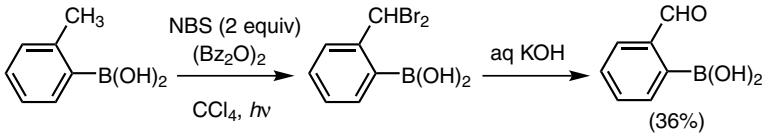

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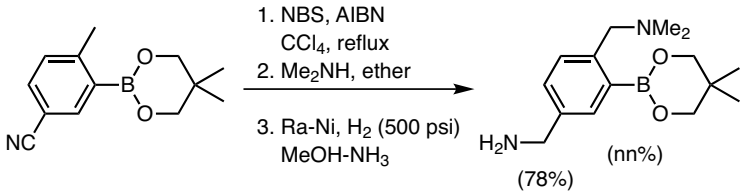
Figure 1.27 Chemoselective oxidation reactions involving boronic acid derivatives.



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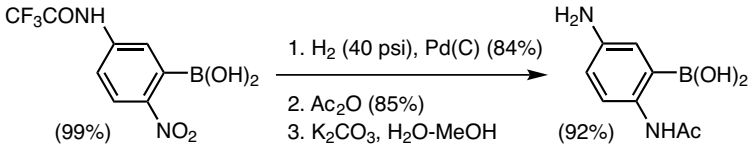
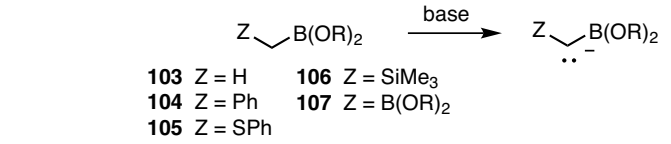


(1.48)

Figure 1.28 Chemoselective reduction reactions involving boronic acid derivatives.

1.3.8.3 Generation and Reactions of α-Boronyl-Substituted Carbanions and Radicals

Carbanions adjacent to a boronate group can be generated by two general approaches: direct deprotonation, or metalation by replacement of an α-substituent. Direct deprotonation of simple alkylboronic esters like 2,4,4,5,5-pentamethyl-1,3,2-dioxaborolane (**103** with $(RO)_2 = OCMe_2CMe_2O$, Equation 1.49 in Figure 1.29) is not possible even with strong bases like LDA or lithium 2,2,6,6-tetramethylpiperidide (LiTMP) [349]. An activating group must be present next to the boronate, and it has



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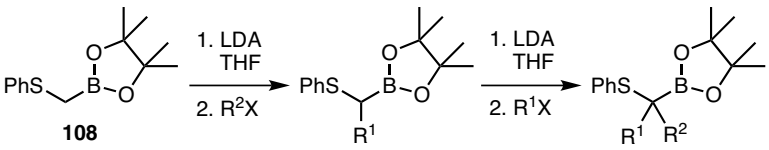

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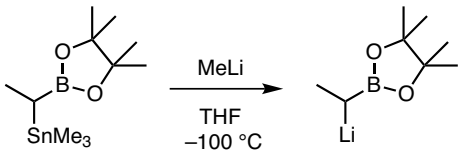

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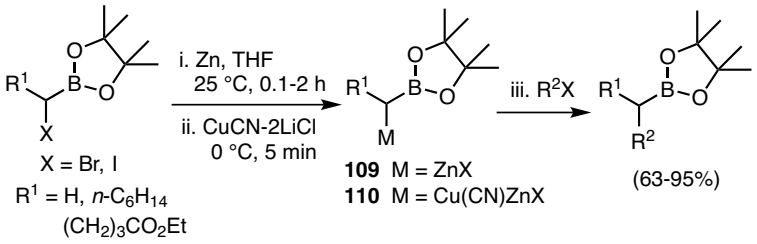

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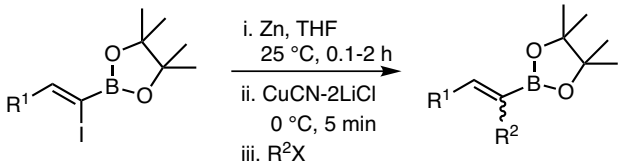


(1.53)

Figure 1.29 Formation and reactions of boronyl-substituted carbanions.

been shown that phenyl [349], thioether [396], trimethylsilyl [347, 397], triphenylphosphonium [397], and another boronate group [349] are all suitable in this role (**104**–**107**, Equation 1.49). Relatively hindered bases and a large boronic ester are preferable in order to favor C–H abstraction over the formation of a B–N ate adduct. For example, the carbanion of bis(1,3,2-dioxaborin-2-yl)methane (**107** with $(RO)_2 = O(CH_2)_3O$) can be generated by treatment with LiTMP (1 equiv) and 1 equiv of the additive tetramethylethylenediamine (TMEDA) in tetrahydrofuran (−78 to 0 °C) [349]. Some of these species can be alkylated efficiently with primary halides and tosylates. Propanediol bisboronate **107** ($(RO)_2 = O(CH_2)_3O$) and the useful α-phenylthio derivative **108**, deprotonated with LDA, can even be alkylated twice in a sequential manner (Equation 1.50) [396]. The anion of **108** was also reacted with epoxides and lactones, and more recently it was used in the synthesis of functionalized boronic acid

analogues of α-amino acids [398]. The carbanions of *gem*-diboronic esters **107** and α-trimethylsilyl pinacolboronate (**106** with $(RO)_2 = O(CH_2)_3O$) undergo other transformations and also behave as substituted Wittig-like reagents by adding to aldehydes or ketones to provide alkenylboronates (e.g., entries 35 and 36, Table 1.4) [348], which can also be oxidized and hydrolyzed to provide the homologated aldehydes [348, 399]. One drawback to the use of **107** is its low-yielding preparation. The corresponding carbanion can also be accessed by reaction of tris(dialkoxyboryl)methanes with an alkyllithium, but this approach lacks generality [400]. Substituted *gem*-diboronates can be made via a sequential hydroboration of 1-alkynes [401], and their anions are generated by treatment with LiTMP (see entry 36, Table 1.4, for addition to ketones). It has been suggested that bis(1,3,2-dioxaborin-2-yl)methane (**107** with $(RO)_2 = O(CH_2)_3O$) is slightly more acidic than triphenylmethane (pK_a 30.6 in DMSO) [349], which confirms the rather weak stabilizing effect of a boronate group compared to a carboxyester (pK_a of dimethylmalonate ~13). The calculation of Huckel delocalization energies confirmed that a boronate group is indeed slightly more stabilizing than a phenyl group (pK_a of diphenylmethane = 32.6 in DMSO), and the calculation of B–C pi-bond orders indicated a very high degree of B–C conjugation in the carbanion [349]. This suggestion appears to be in contradiction with the apparently modest degree of B−C pi-overlap in alkenyl and aryl boronates discussed in Section 1.2.2.1; however, those cases concern neutral species.

Other methods for the generation of α-boronyl carbanions include transmetalations such as the lithiation of an α-trimethylstannyl derivative (Equation 1.51, Figure 1.29) [402] and the formation of the corresponding organozinc or organocopper species from α-bromo or α-iodo alkylboronates (Equation 1.52) [403]. In the latter example, the mildness of the zinc and copper organometallic intermediates expands the range of compatible functional groups compared to the corresponding organolithium intermediates described above. Thus, reagents **109** and **110**, even with a carboxyester-containing side chain as R^1 substituent, were reacted with a variety of electrophiles such as allylic halides, aldehydes, and Michael acceptors in good to excellent yields (Equation 1.52) [403]. Likewise, the related sp^2 1,1-bimetallics can be generated from 1-iodoalkenylboronic pinacol esters albeit with loss of stereochemical integrity of the olefin geometry (Equation 1.53) [404]. In one example, the Negishi coupling of a 1-iodozincalkenylboronate with an alkenyl iodide partner led to the formation of a 2-boronylbutadiene.

1.3.8.4 Reactions of α-Haloalkylboronic Esters

One of the most powerful methods for modifying alkylboronic esters involves the nucleophilic attack and 1,2-rearrangement on α-haloalkylboronic esters (**111**) (Figure 1.30). The addition of organometallic species to these boronic esters induces a facile boron-promoted displacement (Equation 1.54). Heteroatom-containing nucleophiles as well as organometallic reagents can be employed in this substitution reaction. Conversely, the addition of α-haloalkyl carbanions to alkyl- and alkenylboronic esters leads to the same type of intermediates and constitutes a formal one-carbon homologation of boronic esters (Equation 1.55). Sulfides from the addition of carbanions of α-thioethers can also undergo this rearrangement in the presence of

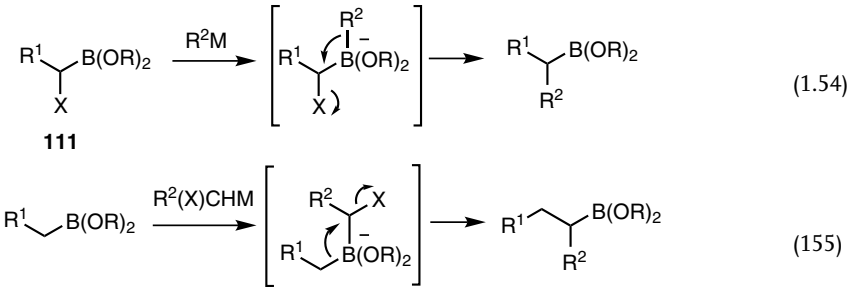
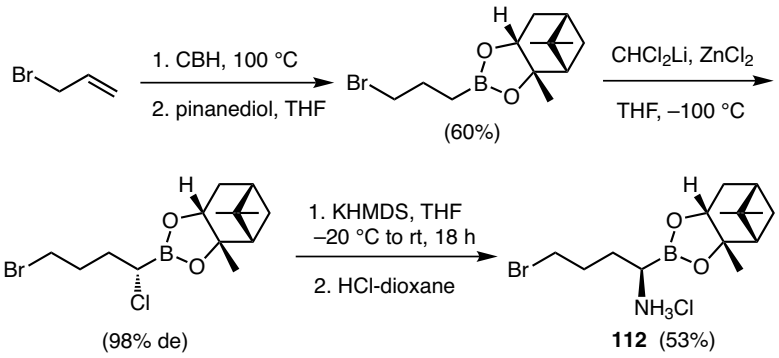


Figure 1.30 Substitution reactions of α-haloalkylboronic esters.

mercuric salts [405]. A very efficient asymmetric variant of this chemistry was developed to allow the synthesis of chiral α-chloroalkylboronates, which can further undergo substitution reactions with a broad range of nucleophiles [406]. These α-chloroboronates are obtained in very high enantiomeric purity through the Matteson asymmetric homologation reaction, which features the $ZnCl_2$-promoted addition of dichloromethyllithium to the boronates of pinanediol and certain C2-symmetrical 1,2-diols. This elegant methodology was used in the synthesis of complex natural products, and is at the cornerstone of the design and preparation of α-acylaminoalkylboronic acid enzyme inhibitors. As exemplified with the synthesis of **112** (Scheme 1.2), α-aminoalkylboronic esters are obtained via the displacement of α-chloroalkylboronates with hexamethyldisilazide anion. This example also emphasizes the powerful neighboring group effect of boron, which allows selectivity in the addition of Cl_2CHLi in the presence of a primary alkyl bromide [407]. More recently, this chemistry was applied to Hoppe's chiral lithiated carbamates (X = $OCONMe_2$ in Equation 1.55) [408], and the applications of these methods in stereoselective synthesis are described in detail in Chapter 10.



Scheme 1.2 Application of the Matteson asymmetric homologation to the synthesis of a chiral α-aminoboronic ester.

1.3.8.5 Other Transformations

Several other reactions can be performed on free boronic acid compounds and the corresponding esters while preserving the boronyl group. The nitration of free arylboronic acids under fuming nitric acid and concentrated sulfuric acid has been known since the 1930s [70]. The use of low temperatures (e.g., Equation 1.56, Figure 1.31) is recommended in order to minimize protodeboronation (Section 1.2.2.5.3) [395, 409]. Other successful transformations of arylboronic acids that preserve the boronyl group include diazotization/hydrolysis [203], bromination [410], iodination (Equation 1.57) [411], and nucleophilic aromatic substitutions [203]. Pinacol arylboronates can be halogenated using a gold-catalyzed halogenation with halosuccinimides [412]. In the context of developing the phase switch synthesis concept already described (Section 1.3.8), reactions such as reductions, oxidations, amidations, Wittig olefinations, cross-metathesis, and others were also found to be compatible with boronic acids [392]. Azide-alkyne cycloadditions require

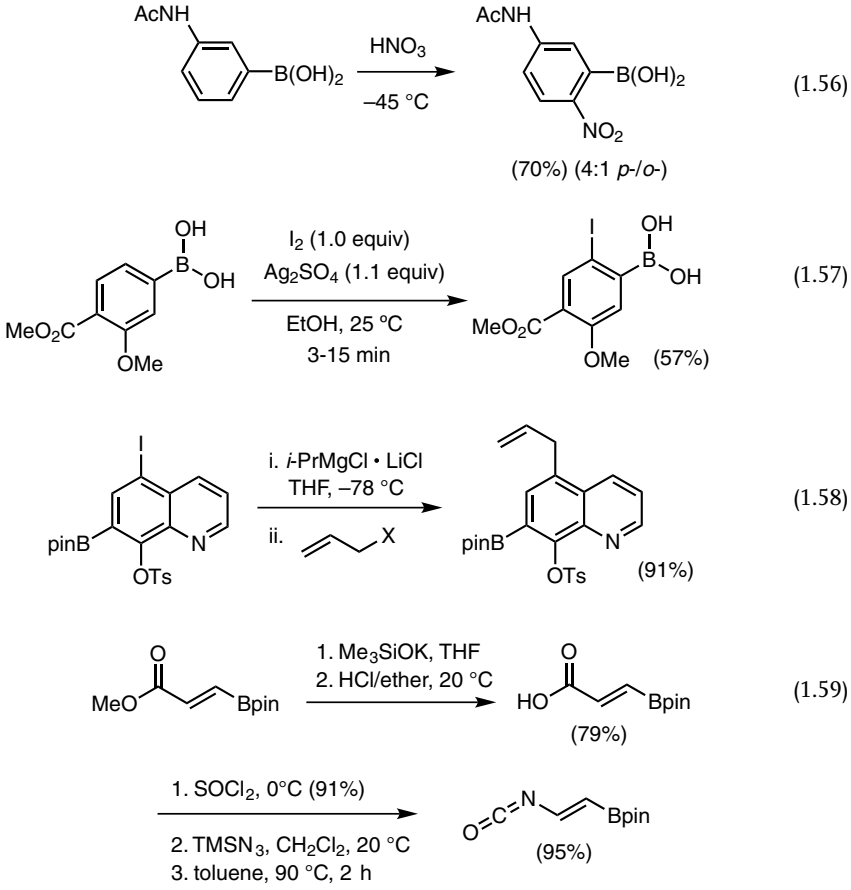
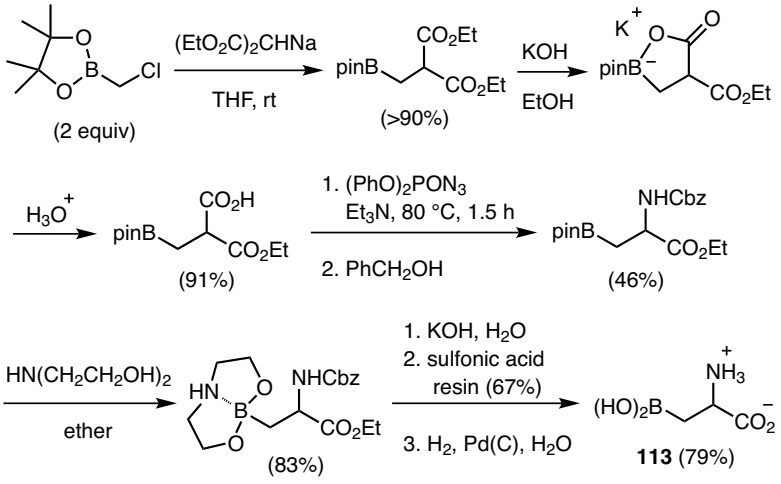


Figure 1.31 Other chemoselective reactions compatible with boronic acid derivatives.

a copper catalyst that may insert into the B–C bond of arylboronic acids, but the addition of fluoride anion provides in situ protection [413]. Unless a special protecting group is employed, metalations of halides in the presence of a boronic acid or the corresponding pinacol esters are difficult due to the electrophilic properties of the boron atom [414]. Exceptionally, pinacol arylboronates containing an iodo substituent can undergo a successful iodine–magnesium exchange under conditions developed by Baron and Knochel, followed by electrophilic trapping (Equation 1.58) [415].

Schrock carbene formation is compatible with arylboronates [92], and radical additions to allyl or vinylboronates provide useful, functionalized alkylboronic esters [416]. Some alkenylboronates can be isomerized to allylboronates in high yields under Ru or Ir catalysis [417]. Pinacol alkenylboronates are robust enough to tolerate a number of transformations such as ester hydrolysis and a Curtius rearrangement (Equation 1.59, Figure 1.31) [418]. Various addition and cycloaddition chemistry of alkenyl- and alkenylboronic acid derivatives are possible, including radical additions, cyclopropanation, and [4 + 2] cycloadditions [258, 359]. Interestingly, pinacol aryl- and alkenylboronates containing a racemic secondary alcohol can be resolved using a lipase enzyme [419].

Alkylboronic esters can also tolerate a wide range of conditions, and problems, if any, are usually encountered in the purification steps rather than with the actual chemistry. The synthesis of 2-amino-3-boronopropionic acid, the boronic acid analogue of aspartic acid (**113**, Scheme 1.3), which included reactions such as carbethoxyester hydrolysis, a Curtius rearrangement, and hydrogenolysis, convincingly illustrates the range of possibilities [420]. Unlike the α-aminoalkylboronic acids, homologous (β-amino) compound **113** is stable and is thought to exist as an internal chelate or a chelated dimer in aqueous solution. Likewise, the lithium



Scheme 1.3 Synthesis of **113**, the boronic acid analogue of aspartic acid.

enolate of 3-oxo alkylboron pinacolates can be formed with LDA and exists in a *Z* chelated form [421].

1.3.8.6 Protection of Boronic Acids for Orthogonal Transformations

There are situations where free boronic acids and standard boronic esters such as pinacolates are not suitable to permit orthogonal reactivity. In situ protection of pinacol esters with alkoxide ligands can be helpful [418c], but permanent protection is a more general strategy. Toward this end, derivatives such as the large ester **42**, diethanolamine adducts **43**, trifluoroborate salts [194], *N*-methyldiaminoacetate (MIDA) **55** [156], and 1,8-diaminonaphthalene (dan) adducts **66** [171] have been developed (Figure 1.32). As shown in Equation 1.60 (Figure 1.33), the scope of compatible transformations can be further increased with the help of a bulky boronate ester to effectively protect the susceptible boron center in oxidations, reductions, and other reactions [120]. These boronates tolerate additions of organometallics onto aldehydes [422], where they can induce stereoselectivity and can also serve in the preparation of cyclopropylboronates [120c]. Boronates **42**, however, are difficult to cleave and are rather removed through a C–B bond transformation. Protection of the boronyl group as a diethanolamine ester allows a clean bromine/lithium exchange [423], which was used in the preparation of *para*- and *meta*-chlorosulfonyl arylboronic acids after trapping with sulfur dioxide (Equation 1.61, Figure 1.33) [423b]. Direct deprotonation of polyfluorinated arylboronic diethanolamine esters was reported [424]. Trifluoroborate salts are tolerant of a wide variety of transformations (see Section 1.2.3.8 and Chapter 11). Likewise, aryl and alkenyl MIDA boronates described in Section 1.2.3.3 can tolerate a wide complement of transformations and can even be carried out through multistep syntheses [425], although their main use is as masking groups in cross-coupling chemistry (Equation 1.62) [426]. Both MIDA boronates **55** [155, 426] and the 1,8-diaminonaphthalene adducts **66** [171, 427] have been employed successfully in iterative cross-coupling strategies to assemble oligoarenes (Scheme 1.4). A derivative of **66** may be used as an *ortho*-directing group for transition metal-catalyzed C–H activation/silylation [428].

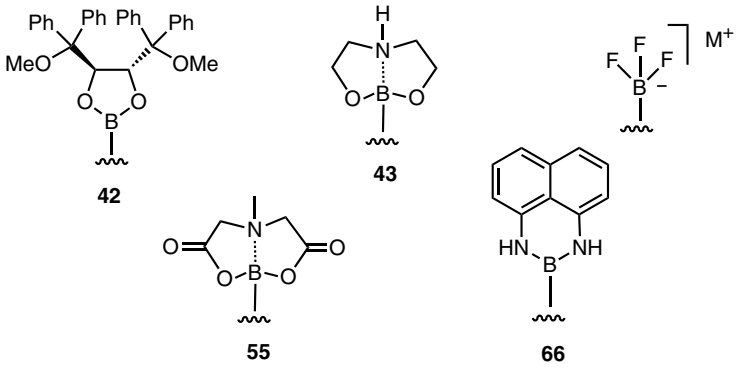
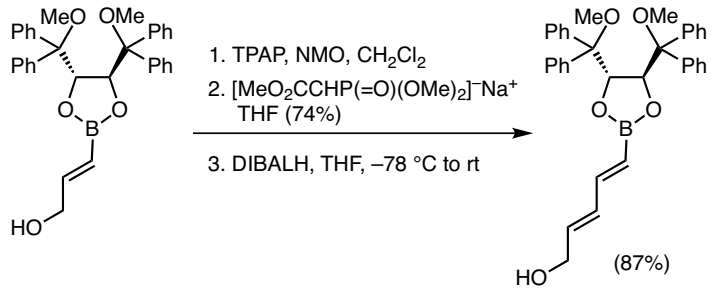


Figure 1.32 Common protecting and masking groups for boronic acids.



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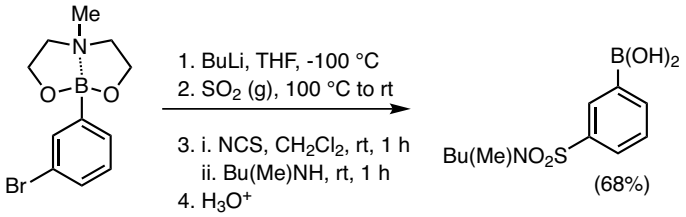

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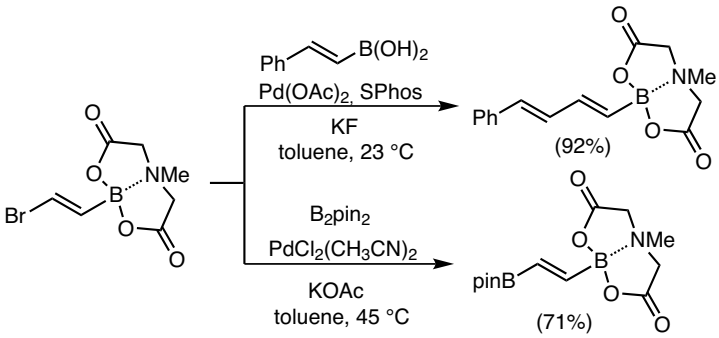

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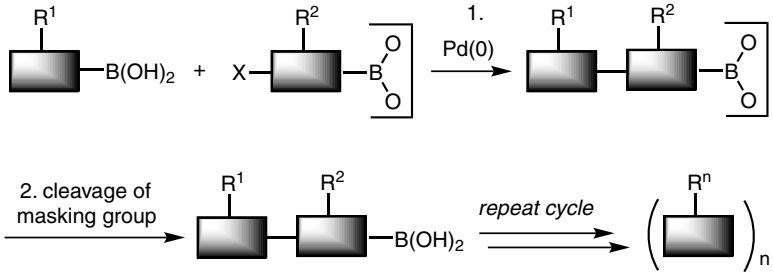
Figure 1.33 Examples of selective transformations on protected boronic acids.



Scheme 1.4 Iterative synthetic scheme for oligoarenes using masked boronic acids.

1.4 Isolation and Characterization

As discussed in Section 1.2.2.2, the polar (and often amphiphilic) character of boronic acids tends to make their isolation and purification a difficult task. In some cases,

nonpolar organic solvents may be used to precipitate small boronic acids dissolved in a polar organic solvent. At higher pH values where the hydroxyboronate species is predominant (Section 1.2.2.4.1), boronic acids may, however, be entirely miscible in water. For this reason, when extracting boronic acids from aqueous solutions, it is desirable to adjust the pH of the water phase to a neutral or slightly acidic level and to use a polar organic solvent for an efficient partition. The use of aqueous conditions is to be avoided for amphoteric boronic acids containing amino substituents, as they are soluble in water in the entire pH range (at pH $>$ 8, the hydroxyboronate species is predominant, and at lower pH, the amine is protonated). The phase switch system with aqueous sorbitol described in Section 1.3.8 may be employed for isolating boronic acids or eliminating nonpolar impurities [392]. It is important to realize that commercial samples of boronic acids may contain various amounts of residual boric acid, which is silent in ^{1}H NMR spectroscopy but can be detected by ^{11}B NMR. Boric acid can usually be separated from boronic acids through a partition between water and chilled diethyl ether. In addition to these potential difficulties in isolating boronic acids, their tendency to form oligomeric anhydrides further complicates their characterization. To palliate these problems, boronic acids are often purified and characterized as esters. The following section provides a summary of useful methods and generalizations for the isolation and characterization of boronic acids and boronic esters.

1.4.1
Recrystallization and Chromatography

Most boronic acids can be recrystallized with ease. The choice of recrystallization solvent, however, greatly affects the relative proportions of free boronic acid and its corresponding anhydrides in the purified solid. Santucci and Gilman found that acids are usually obtained from aqueous solutions (i.e., water or aqueous ethanol), and anhydrides predominate when nonpolar recrystallization solvents like ethylene dichloride are employed [429]. Recrystallization in benzene gives some dehydration, but to a lesser extent. Several other solvents have been used for the recrystallization of arylboronic acids, including two-solvent systems. Most boronic acids are soluble in polar solvents like ether, methylene chloride, and ethyl acetate and are insoluble in pentane or hexanes. Much like carboxylic acids, most boronic acids interact strongly with silica gel. Depending on the degree of hydrophobicity of the boron substituent, chromatography and TLC on silica gel are possible despite the high retentivity of boronic acids. To this end, the eluent mix of 20–50% ethyl acetate/hexanes is generally suitable for most arylboronic acids, and those with additional polar groups may require methanol or acetic acid as a coeluent. Some electron-rich arylboronic acids tend to deboronate faster on silica gel; thus, prolonged exposure to silica from lengthy separations should be avoided. In such cases, filtration through a short plug of silica using acetone as coeluent [430] or the use of a polar eluent mixture made of CH_2Cl_2 and EtOAC was found suitable [409]. For example, a highly lipophilic trienylboronic acid was conveniently purified by silica gel chromatography [273].

1.4.2
Solid Supports for Boronic Acid Immobilization and Purification

Recently, the increasing popularity of boronic acids as synthetic intermediates has motivated the development of solid supports and linkers to allow their immobilization and facilitate purification operations or derivatization (Figure 1.34). The appeal of these methods is particularly apparent in view of the difficulties often encountered in the isolation of pure boronic acids from both aqueous and organic solvent systems.

1.4.2.1 **Diethanolaminomethyl Polystyrene**

Diol-based insoluble polystyrene resins that can form supported boronic esters are obvious choices for immobilizing boronic acids. Hall and coworkers reported the first example of solid support for boronic acids, the diethanolaminomethyl polystyrene resin (DEAM-PS, **114** in Figure 1.34), which is now commercially available [431, 432]. The immobilization of alkyl-, alkenyl-, and arylboronic acids with this resin is straightforward, consisting simply of mixing a slight excess of DEAM-PS, as a suspension, in an anhydrous solution containing the boronic acid [431a]. Tetrahydrofuran was found to be the solvent of choice as it dissolves most boronic acids. It is noteworthy that no azeotropic removal of the water released is needed, which comes as a benefit of the B–N coordination in the resulting adducts and of the highly hydrophobic nature of this polystyrene support. This simple procedure can be employed for purifying boronic acids (Equation 1.63, Figure 1.34) or for scavenging excess reagent from crude reaction mixtures [433], including amphoteric ones that would be otherwise difficult to isolate from aqueous solvent systems. Following

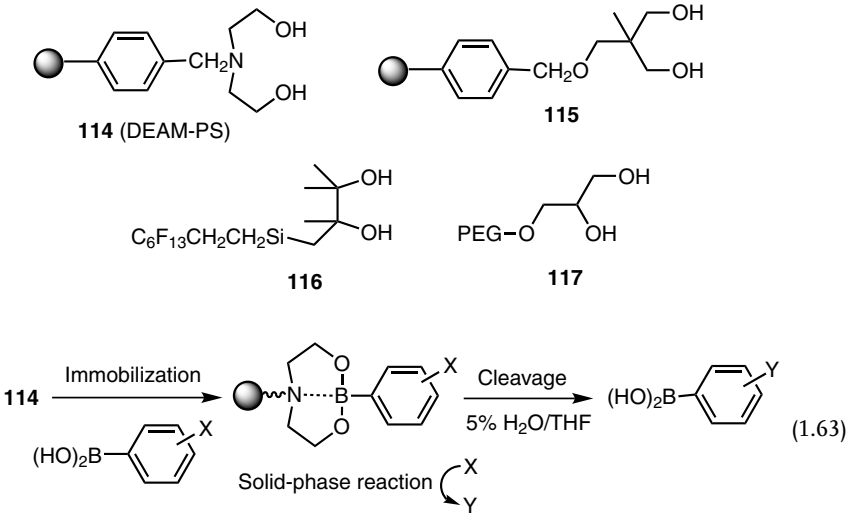


Figure 1.34 Diol-based supports for boronic acid immobilization and purification. Solid-phase immobilization and derivatization of boronic acids using *N,N*-diethanolaminomethyl polystyrene (DEAM-PS).

resin washings, the desired boronic acid can be recovered upon treatment of the resin with a 5–10% solution of water in THF. A wide variety of arylboronic acids were immobilized with the DEAM-PS resin, and it has even been employed successfully in the derivatization of functionalized boronic acids [432]. Thus, amino-substituted arylboronic acids supported onto DEAM-PS were transformed into anilides and ureas, bromomethyl-substituted ones were reacted with amines, formyl-substituted ones were subjected to reductive amination with aldehydes, and carboxy-substituted phenylboronic acids were transformed into amides [432]. All these transformations afford new arylboronic acid derivatives in very high purity directly after cleavage from the resin. The DEAM-PS-supported boronic acids were also employed in the interesting concept of resin–resin transfer reactions (RRTR), whereby a phase transfer agent is used *in situ* to allow the transfer of one supported substrate to another resin-supported substrate. This convergent solid-phase synthetic strategy was applied to the Suzuki-Miyaura cross-coupling [434] and the borono-Mannich reactions [435].

1.4.2.2 Other Solid-Supported Diol Resins

A macroporous polystyrene resin functionalized with a 1,3-diol unit, **115**, was described by Carboni *et al.* [436]. Although the immobilization and subsequent cleavage of boronic acids both require harsher conditions compared to DEAM-PS, this support was also proven useful in the derivatization of functionalized boronic acids, as well as in a number of elegant C–C bond forming/release procedures [437] and a traceless cleavage of arenes [438]. Analogous pinacol-like linkers were also described, although preattachment of the boronic acid prior to immobilization was required in these examples [439]. A ROMP gel diol was employed for the immobilization of allylboronates [440]. A catechol-functionalized polystyrene resin was also found to be effective in the immobilization and derivatization of functionalized arylboronic acids [441].

1.4.2.3 Soluble Diol Approaches

Fluorous-phase purification methodologies using fluoroalkyl-tagged substrates combine the advantages of homogeneous reaction conditions of solution-phase reactions with the ease of purification of solid-phase methods. In this regard, pinacol-like and other diol-based polyfluoroalkyl linkers such as **116** were described [442]. The resulting fluorous boronates were employed in a variety of transformations and allowed a facile purification by simple partition between fluorous and organic solvents. A dendritic high-loading polyglycerol, **117**, was shown to be effective in immobilizing arylboronic acids and in facilitating the purification of biaryl products from homogeneous Suzuki cross-coupling reactions [443].

1.4.3 Analytical and Spectroscopic Methods for Boronic Acid Derivatives

1.4.3.1 Melting Points, Combustion Analysis, and HPLC

The difficulty in measuring accurate and reproducible melting points for free boronic acids has long been recognized [444]. Rather than true melting points, these measurements are often more reflective of dehydration or decomposition

points [212, 445]. The lack of reproducibility for a given boronic acid may originate from the water contents of the sample used, which affects the acid–anhydride transition. Moreover, as mentioned above, the water content also depends on the recrystallization solvent [429]. For these reasons, it is often more appropriate to report melting points of boronic acids as their diethanolamine esters (Section 1.2.3.2.1). Likewise, combustion analysis of free boronic acids may provide inaccurate results depending on the recrystallization method. Reverse-phase HPLC chromatography may be used for analyzing boronic acids and esters, albeit on-column hydrolysis can complicate the analysis of boronic esters. Fast methods suitable to arylboron pinacol esters have been reported [446].

1.4.3.2 **Mass Spectrometry**

One useful diagnostic detail in the mass spectrometric analysis of boronic acid derivatives is the observation of boron's isotopic pattern, which is constituted of ^{10}B (20% distribution) and ^{11}B (80% distribution). On the other hand, unless other functionalities help increase the sensitivity of a boronic acid-containing compound, it is often difficult to obtain intense signals with most ionization methods due to the low volatility of these compounds. This problem is exacerbated by the facile occurrence of gas-phase dehydration and anhydride (boroxine) formation in the ion source. Electrospray ionization in the negative mode tends to provide the best results with minimal fragmentation, the $[M–H]^-$ and $[2M–H_2O–H]^-$ fragments being most common using methanol, acetonitrile, water, or mixtures thereof as the most effective solvent systems. For amino-substituted boronic acid compounds, the ESI positive mode is usually effective, giving $[M + H]^+$ and $[M + Na]^+$ as common fragments. To minimize thermal reactions and improve volatility, cyclic boronates may be employed. These derivatives were even made on analytical scale [447]. The fragmentation patterns of various *para*-substituted arylboronic esters of 1,2-ethanediol were studied using electron impact ionization and several deboronative fragmentation pathways were observed [448]. The nature of the *para*-substituent was found to have a marked influence. In another study by GC-MS, *ortho*-substituents were found to interact strongly during fragmentation [447]. Boropeptides, a popular class of enzyme inhibitors (Section 1.6.5), and phenylboronic acid were characterized by positive-ion ammonia chemical ionization with different diols as benchtop derivatization agents [449].

1.4.3.3 **Nuclear Magnetic Resonance Spectroscopy**

Boron compounds, including boronic acid derivatives, can be conveniently analyzed by NMR spectroscopy [450]. Of the two isotopes, ^{11}B is the most abundant (80%) and possesses properties that are more attractive toward NMR. Specifically, these attributes include its lower resonance frequency, spin state (3/2) and its quadrupole moment, a wide range of chemical shifts, and its relatively high magnetic receptivity (16% of ^1H). Most boronic acids are soluble in dimethylsulfoxide (DMSO-d6), and it is a particularly effective NMR solvent ($-B(OH)_2$ resonance $\sim$8.3 ppm). When analyzing boronic acids in nonhydroxylic solvents by NMR spectroscopy, it is often necessary to add a small amount of deuterated water (e.g., one or two drops) to the sample in order to break up the oligomeric anhydrides. Alternatively, analysis in

anhydrous alcoholic solvents such as methanol will allow observation of the *in situ* formed methanolic ester. Observation of the ^{11}B nucleus against a reference compound (e.g., BF_3) is straightforward with modern instruments, and can be especially revealing of the electronic characteristics [34] and coordination state of the boronate moiety. The boron resonance of free boronic acids and tricoordinate ester derivatives is generally detected in the 25–35 ppm range, and tetracoordinate derivative such as diethanolamine esters are detected at around 10 ppm [451]. In ^{13}C analysis, carbons next to the boron atom tend to be broadened often beyond the limits of detection due to the quadrupolar relaxation of ^{11}B. Consequently, with aromatic boronic acids, the signal from the quaternary carbon bearing the boron atom can be very difficult to observe over the background noise.

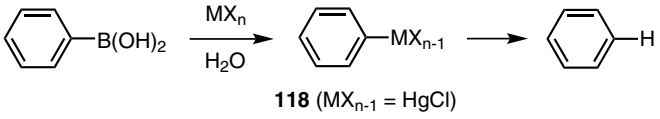
1.4.3.4 Other Spectroscopic Methods

In spite of their limited structure determination capabilities, ultraviolet and infrared spectroscopies were determinant characterization techniques in the early days of boronic acid research [429]. Noted IR absorptions are the strong H-bonded OH stretch (3300–3200 cm^{-1}), and a very strong band attributed to B–O stretch (1380–1310 cm^{-1}). IR is particularly diagnostic of the presence of boronic anhydrides. Upon anhydride (boroxine) formation, the OH stretch disappears and a new strong absorption appears at 680–705 cm^{-1} [75].

1.5 Overview of the Reactions of Boronic Acid Derivatives

1.5.1 Metalation and Metal-Catalyzed Protodeboronation

In 1882, Michaelis and Becker described the preparation of phenylmercuric chloride (**118**) from the reaction of phenylboronic acid and aqueous mercuric chloride (Equation 1.64, Figure 1.35) [228b]. Benzylboronic acid was transformed to benzylmercuric chloride in the same manner, and both compounds were found to resist hydrolysis under the conditions of their preparation. Mechanistic studies later showed that this reaction proceeds through the hydroxyboronate ion [452]. Catechol and pinacol alkenylboronic esters were also found to be transmetalated into the corresponding organomercurial derivative with retention of configuration [453, 454]. One of the early observations on the reactivity of arylboronic acids was the realization that a number of metal ions (other than Hg(II)) can induce protodeboronation in water, presumably via the intermediacy of an arylmetal species (Equation 1.64). Thus, Ainley and Challenger found that hot solutions of phenylboronic acid with copper sulfate, cadmium bromide, or zinc chloride produce benzene [70]. As phenylboronic acid is stable to dilute hydrochloric acid, it was deduced that the deboronation occurred through the formation of transmetalated intermediates similar to **118** (Figure 1.35) and their reaction with water, and not from the possible release of acid by hydrolysis of the metal salt. Instead of giving benzene, cupric chloride and bromide were found to provide the respective phenyl chloride and bromide [70].



118 (MX_{n-1} = HgCl) (1.64)

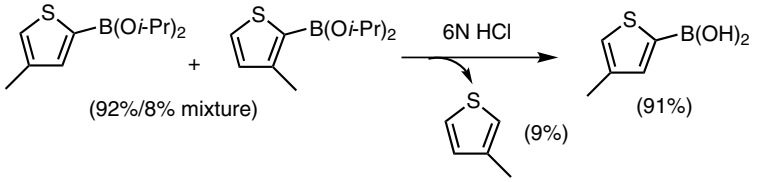


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Figure 1.35 Protodeboronation of boronic acids.

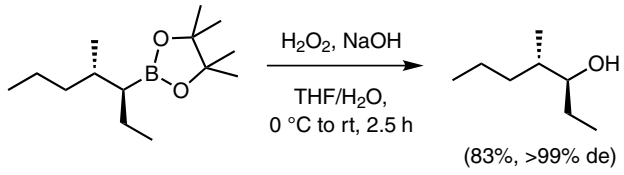
Halide salts of beryllium, magnesium, and calcium did not react with phenylboronic acid [70]. Arylboronic acids were transformed into arylthallium derivatives in a similar fashion [455], and alkylboronic acids were found to be unreactive under the same conditions [86]. Ammonical solutions of silver nitrate also induce protodeboronation of arylboronic acids with production of silver oxide [202]. Aliphatic boronic acids behave differently and rather tend to undergo a reductive coupling to give the dimeric alkane products [85]. Kuivila *et al.* studied the mechanism of metal ion catalysis in the aqueous protodeboronation of arylboronic acids [456]. Substituent effects and the influence of pH were investigated, and both base and cadmium catalysis pathways were evidenced for this reaction. The order of effectiveness of the different metal ions at effecting deboronation was established to be Cu(II) > Pb (II) > Ag(I) > Cd(II) > Zn(II) > Co(II) > Mg(II) > Ni(II). Boron–zinc exchange with boronic acids is a well-established synthetic process [457]. More recently, bismuth [458] and gold salts [459] were found to undergo a B–M transmetalation.

The silver nitrate-promoted protodeboronation method can be synthetically useful [438]. The regioselective protodeboronation of an isomeric mixture of heterocyclic boronic acids was employed as a separation strategy (Equation 1.65) [460]. On a synthetic chemistry standpoint, however, reaction of the metalated intermediates with electrophiles other than a proton is usually more attractive. Indeed, one of the most important recent developments in boronic acid chemistry strove from the discoveries that transition metals such as palladium(0), rhodium(I), and copper(I) can oxidatively insert into the B–C bond and undergo further chemistry with organic substrates. These processes are discussed in Sections 1.5.3 and 1.5.4 and several other chapters.

1.5.2 Oxidative Replacement of Boron

1.5.2.1 Oxygenation

The treatment of arylboronic acids and esters with alkaline hydrogen peroxide to produce the corresponding phenols was first reported more than 75 years ago [70]. The oxidation of alkyl- and alkenylboronic acid derivatives leads to alkanols [42]



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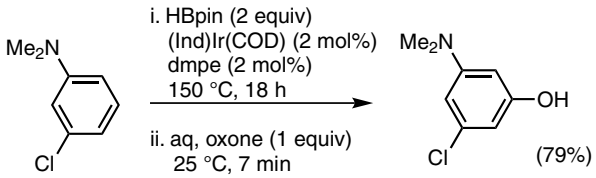

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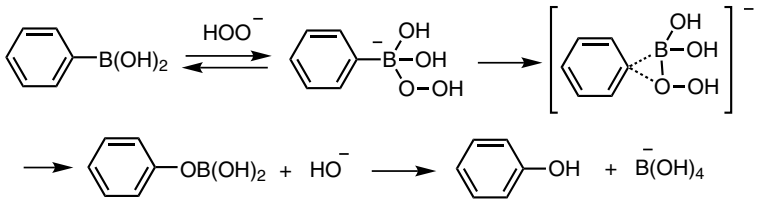

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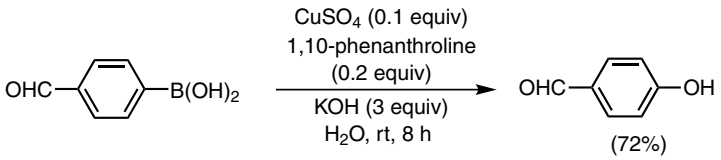

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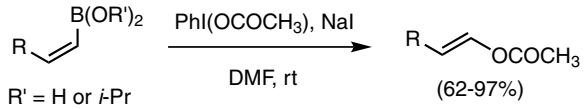


(1.70)

Figure 1.36 Oxidation of boronic acids (esters).

and aldehydes/ketones, respectively [95, 309a, 348, 399]. With chiral α-substituted alkylboronates, the reaction proceeds by retention of configuration (Equation 1.66, Figure 1.36) [137, 461]. In fact, the oxidation of boronic acids and esters is a synthetically useful process in the preparation of chiral aliphatic alcohols via asymmetric hydroboration of alkenes [369] or from the Matteson homologation chemistry [406]. On the other hand, the oxidation of arylboronic acids is usually not a popular and economical approach for preparing phenols. It was reported, however, that a one-pot C–H activation/borylation/oxidation sequence gives access to *meta*-substituted phenols that would be difficult to obtain by other means (Equation 1.67) [462]. The mechanism of the aqueous basic oxidation of phenylboronic acid

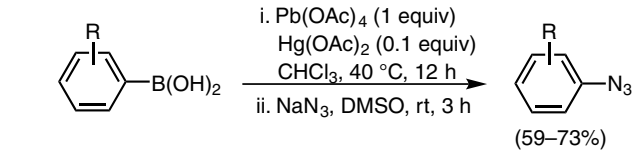
was investigated by Kuivila [463]. The rate is first order each in boronic acid and hydroperoxide ion, which led the authors to propose the mechanism of Figure 1.36 (Equation 1.68). The transition state features a boron–to–oxygen migration of the ipso-carbon. Milder oxidants like anhydrous trimethylamine *N*-oxide [464], oxone [465], sodium perborate [466], and hydroxylamine [467] can also be employed for the oxidation of most types of boronic acid derivatives. It is noteworthy that perborate was found to give a cleaner oxidation of alkenylboronic acids into aldehydes compared to hydrogen peroxide [399]. Recently, mild room-temperature copper-catalyzed hydroxylations of arylboronic acids have appeared (Equation 1.69) [468]. Allylic boronic esters can be oxidized using nitrosobenzene with a SE' regioselectivity complementing the use of peroxide [469]. Interestingly, the combined use of diacetoxyiodobenzene and sodium iodide under anhydrous conditions transforms alkenylboronic acids and esters into enol acetates in a stereospecific manner (Equation 1.70) [470].

1.5.2.2 **Amination and Amidation**

Aryl azides can be accessed indirectly from arylboronic acids via *in situ* generated aryllead intermediates (Equation 1.71, Figure 1.37) [471]. A mild procedure for ipso-nitration of arylboronic acids was developed (Equation 1.72), and a mechanism was proposed [472]. Common methods and reagents for electrophilic amination, however, do not affect boronic acids and their esters. These processes require the intermediacy of more electrophilic boron substrates such as borinic acids or dichloroboranes. For example, enantiomerically pure propanediol boronates, which are accessible from the asymmetric hydroboration of alkenes with ipc_2BH followed by the acetaldehyde-promoted workup and transesterification, can be treated sequentially with MeLi and acetyl chloride. The resulting borinic ester is sufficiently electrophilic to react at room temperature with the amination reagent hydroxylamine-*O*-sulfonic acid with retention of stereochemistry to give primary amines in essentially 100% optical purity (Equation 1.73) [473]. The preparation of optically pure secondary amines from alkyl azides also requires the intermediacy of the highly electrophilic dichloroboranes (Equation 1.74) [191], which can be made from boronic esters and monoalkylboranes, as described in Section 1.2.3.6. Intramolecular variants of the reaction with alkyl azides provide access to pyrrolidines and piperidines [474]. A more contemporary amination of arylboronic acids affords primary anilines using a copper oxide catalyst and aqueous ammonia at ambient temperature (Equation 1.75) [475]. A copper-catalyzed coupling with nitrosoarenes gives diaryl amines [476] and a XeF_2-promoted reaction with nitriles gives anilides [477].

1.5.2.3 **Halodeboronation**

1.5.2.3.1 **Arylboronic Acids and Esters** As described above, cuprous chloride and bromide provided the corresponding ipso-substituted phenyl halides from benzeneboronic acid [70]. A modern stepwise one-pot version of these copper-promoted halogenations employs pinacol arylboronates made via transition metal-catalyzed



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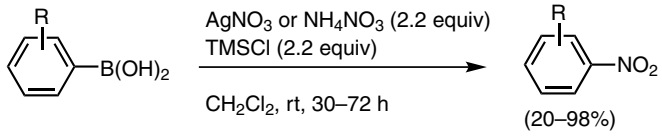

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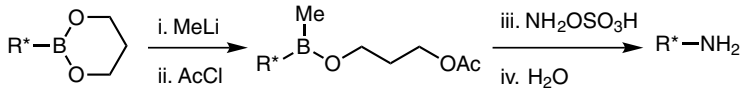

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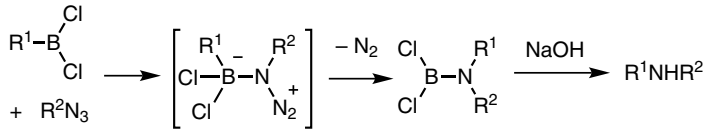

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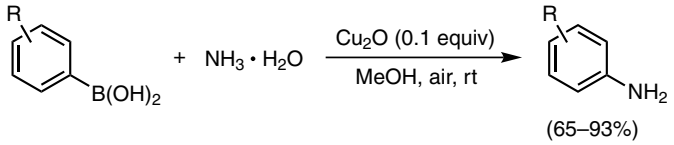

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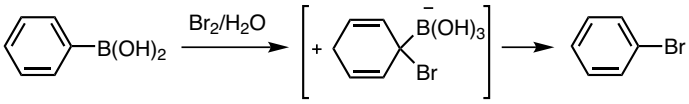
Figure 1.37 Oxidative amination of boronic acid derivatives.

borylation [478]. Arylboronic acids are halodeboronated regioselectively by the action of aqueous chlorine, bromine, and aqueous iodine-containing potassium iodide [70]. Alkylboronic acids do not react under the same conditions [42]. The kinetics of bromonolysis in aqueous acetic acid has been studied by Kuivila and Easterbrook, who found that bases catalyze the reaction [479]. This observation and a Hammett plot of 10 arylboronic acids [480] are consistent with a proposed electrophilic ipso-substitution mechanism involving the usual weakening effect of the C–B bond through formation of a boronate anion (Equation 1.76, Figure 1.38). *N*-Bromo- and *N*-iodosuccinimides convert arylboronic acids to the corresponding aryl halides in good to excellent yields [481]. Most arylboronic acids react in refluxing acetonitrile, whereas the most activated ones such as 2-methoxyphenylboronic acid are iodinated at room temperature. Boronic esters provide significantly lower yields, and *N*-chlorosuccinimide is essentially unreactive even in the presence of bases. The use of 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) under catalysis by sodium methoxide was shown to be an efficient bromodeboronation method for arylboronic acids when acetonitrile is used as the solvent (Equation 1.77, Figure 1.38) [482].



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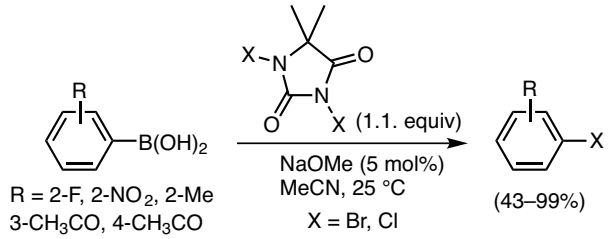

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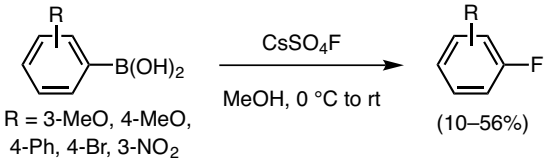

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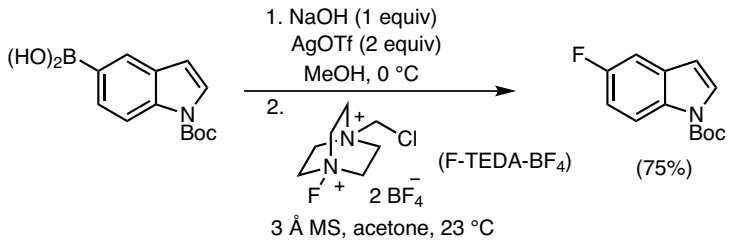

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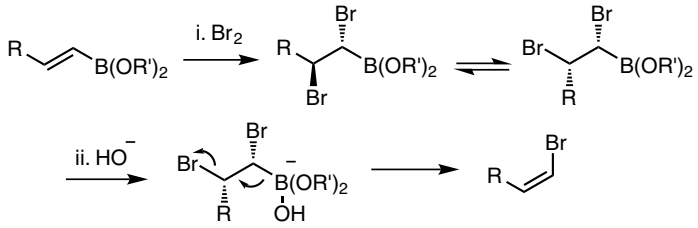
Figure 1.38 Halodeboronation of arylboronic acids.

The corresponding reagent DCDMH leads to the isolation of arylchlorides. The combined use of chloramine-T and sodium iodide in aqueous THF affords aryliodides from 2,2-dimethylpropanediol boronates [483]. Aryltrifluoroborate salts are transformed into bromides by action of n-Bu_4NBr_3 under aqueous conditions [484]. Arylfluorides can be obtained in rather modest yield by treatment of arylboronic acids with cesium fluoroxysulfate ($CsSO_4F$) in methanol (Equation 1.78) [485]. Recently, however, interest in medical applications of positron emission tomography led to improved and more general fluorodeboronation procedures, including stepwise Pd(II)- [486] and Ag(I)-promoted methods (Equation 1.79) [487]. Aryl(phenyl)iodonium salts are formed by treatment of arylboronic acids with trifluoromethanesulfonic acid and diacetoxyiodobenzene in dichloromethane [488].

1.5.2.3.2 **Alkenylboronic Acids and Esters** The sequential treatment of alkenylboronic esters with bromine in ethereal anhydrous solvent and then with sodium hydroxide or alkoxides in a one-pot fashion provides the corresponding alkenyl bromides with inversion of olefin geometry (Equations 1.80 and 1.81, Figure 1.39) [489–491]. A reasonable mechanism to account for the inversion was



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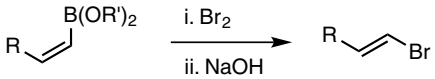

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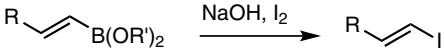

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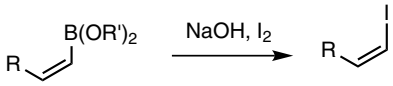

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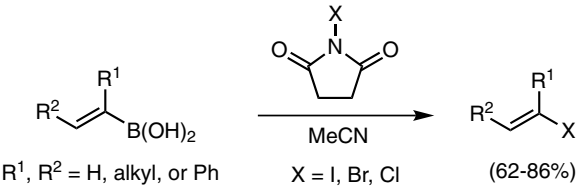

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Figure 1.39 Halodeboronation of alkenylboronic acids (esters).

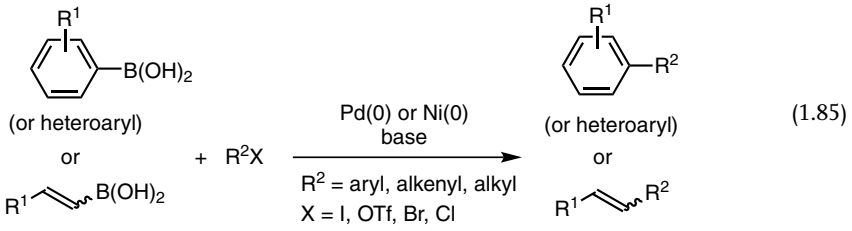
proposed based on the formation of a vicinal dibromide followed by a *trans*-bromodeboronation promoted by the addition of the base (Equation 1.80) [491]. The related iodinolysis process is complementary, giving alkenyl iodides with retention of olefin geometry (Equations 1.82 and 1.83) [492]. The procedure involves the simultaneous action of iodine and aqueous sodium hydroxide, and a tentative mechanism involving the *syn*-deboronation of an iodohydrin intermediate has been proposed to explain the stereochemistry of this reaction [491]. Like the bromination process, however, a sequential treatment of the alkenylboronic acid with iodine and then with sodium hydroxide generally provides the corresponding alkenyl iodides by inversion of geometry [491]. In both cases, boronic acids can be used directly with only 1 equiv of halogen, whereas boronic esters can be transformed effectively with at least 2 equiv of the requisite halogen. The use of ICl and sodium acetate was also demonstrated [493]. The combination of ICl and sodium methoxide as base was found to be more efficient in the case of hindered pinacol alkenylboronates, and both isomers can be obtained selectively from a single *E*-1-alkenylboronate depending on the order of addition [494]. Petasis and Zavialov reported a mild halogenation procedure for various types of alkenylboronic acids using halosuccinimides as

reagents (Equation 1.84, Figure 1.39) [495]. The reactions proceed in acetonitrile at room temperature and provide high yields of alkenyl halide products with retention of olefin geometry. The chlorination variant with *N*-chlorosuccinimide requires the use of triethylamine as a base. The chlorination of alkenylboronic acids was also carried out with chlorine and occurs by inversion of olefin geometry [496].

1.5.3
Carbon–Carbon Bond Forming Processes

1.5.3.1 Transition Metal-Catalyzed Cross-Coupling with Carbon Halides and Surrogates (Suzuki–Miyaura Cross-Coupling)

The ability of boronic acids to undergo C–C bond formation in the presence of a stoichiometric quantity of palladium was recognized in 1975 [272]. A subsequent 1979 *Chemical Communications* paper by Miyaura and Suzuki reported findings generally regarded as the most important discovery in the recent history of boronic acid chemistry [497]. This paper described the palladium(0)-catalyzed coupling between alkenyl boranes or catecholates and aryl halides, in the presence of a base, providing arylated alkene products in high yields. Soon thereafter, a seminal paper on the synthesis of biaryls by coupling of phenylboronic acid with aryl bromides and halides was reported (Equation 1.85, Figure 1.40) [498]. Since then, significant improvements of this important synthetic methodology have been made through optimization of the different reaction parameters such as catalyst, ligands, base, solvent, and additives.



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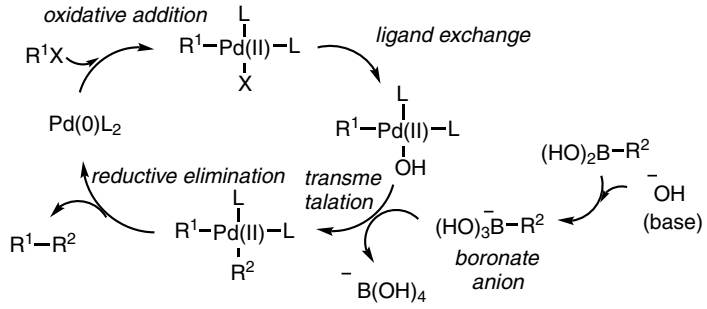
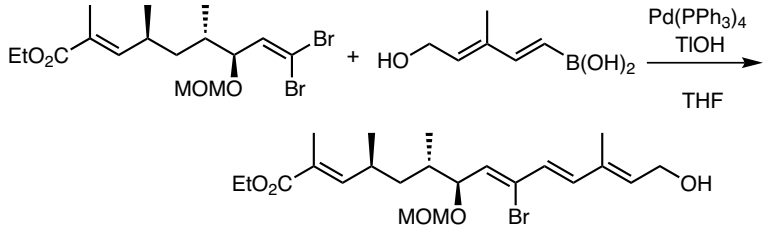


Figure 1.40 Transition metal-catalyzed coupling of boronic acids (esters) with carbon halides/triflates (Suzuki–Miyaura cross-coupling reaction). *Bottom*: Accepted mechanism in aqueous conditions.

These advances have been reviewed regularly [499], including applications in natural product synthesis [499g]. All the contemporary aspects of the Suzuki–Miyaura cross-coupling reaction are covered in detail in Chapter 4; therefore, only a brief summary is provided in this section. The accepted mechanism for the aqueous basic variant involves oxidative addition of the halide substrate to give a Pd(II) intermediate, followed by a transmetalation, and a final reductive elimination that regenerates the Pd(0) catalyst (Figure 1.40) [500–502]. The two key catalytic intermediates have been observed by electrospray mass spectrometry [503], but ambiguities remain pertaining to the nature of the turnover-limiting step. Although the specific role and influence of the base remain unclear [504], it was suggested that the transmetalation is facilitated by a base-mediated formation of the tetracoordinate boronate anion [505], which is more electrophilic than the free boronic acid (Sections 1.5.1 and 1.5.2). A recent report, however, showed that when a weak base is used in aqueous solvents, transmetalation between a Pd hydroxy complex and trigonal boronic acid is possible [506]. A useful carbonylative variant has also been developed to access benzophenones [507], which can also be produced from the coupling of acid chlorides [508] or anhydrides [509]. Another variant allows the preparation of α,β-unsaturated carboxyesters from alkenylboronic esters [294]. In many of these reactions, a dreaded limitation with some *ortho*-substituted and electron-poor arylboronic acids is the possible occurrence of a competitive protolytic deboronation, which is exacerbated by the basic conditions and the use of a transition metal catalyst (Section 1.5.1). As a result, an excess of boronic acids is often needed, but a method employing a fluorescent dye was proposed as a way to monitor consumption of the boronic acid using a standard handheld UV lamp [510]. Methods to minimize this side reaction were developed, in particular the use of milder bases [511] like fluoride salts [512] and nonaqueous conditions [513]. Recently, a slow-release strategy using MIDA boronates was shown to allow effective coupling of α-heterocyclic and other sensitive boronic acids that are notorious for their tendency to protodeboronate [41]. Competitive homocoupling of the arylboronic acid can compete, but it can also be an attractive process for making symmetrical biaryls [514]. Despite these impediments, the venerable Suzuki–Miyaura cross-coupling reaction has become the most versatile method to synthesize a broad range of biaryl and heteroaryl compounds that find widespread uses as pharmaceutical drugs and materials. The reaction is particularly useful in combination with *ortho*-metalation approaches to generate the arylboronic acid substrate [515]. Alkenylboronic acids and esters, including vinylboronates [516], are also very useful substrates, in particular to access substituted olefins and dienyl moieties commonly encountered in several classes of bioactive natural products [351, 517]. To this end, Kishi and coworkers examined the influence of the base, and developed an optimal variant using thallium hydroxide [350] (Equation 1.86, Figure 1.41) [518]. The Suzuki–Miyaura cross-coupling can be applied to the use of allylic boronic acids [519] and alkylboronic acids [362, 520], including cyclopropylboronic acids [520d], and major recent advances were made with the use of alkyltrifluoroborate salts (Chapter 11) [521]. Hitherto known to be notorious for their tendency to undergo β-hydride elimination, alkyl bromides are now suitable as electrophiles under carefully optimized conditions that even allow couplings of secondary alkyl halides [522] and Csp^3–Csp^3 couplings with alkylboronic acids



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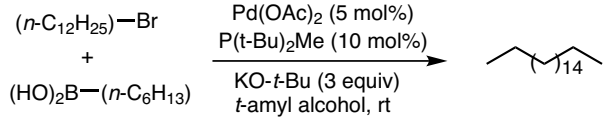

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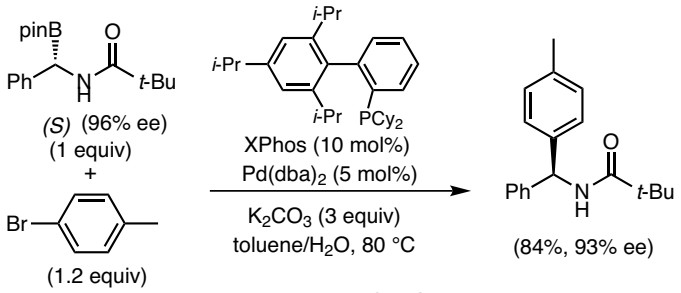

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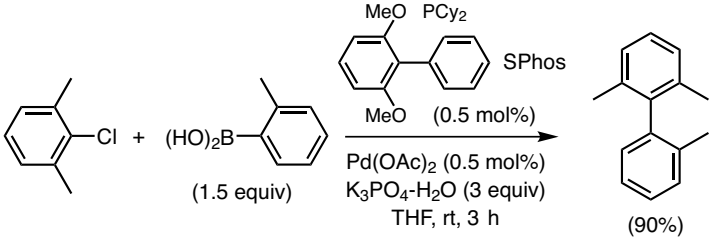

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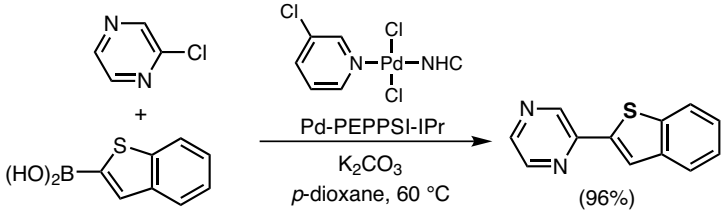

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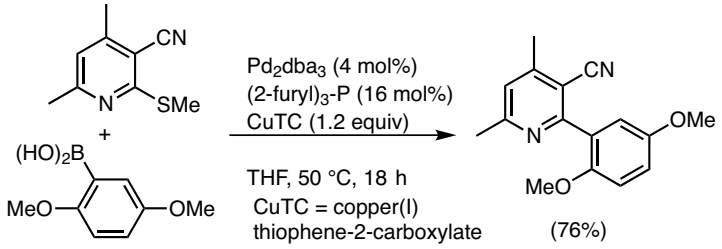

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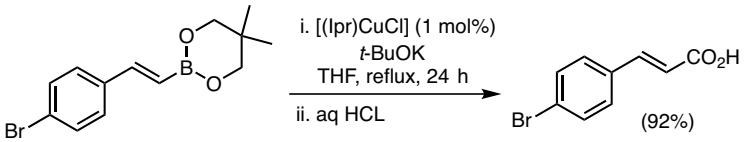
Figure 1.41 Selected examples of Suzuki–Miyaura cross-coupling reactions.

(Equation 1.87) [523]. Methods for stereoselective cross-couplings of optically enriched alkylboronic acids have begun to emerge (Equation 1.88) [524]. The Suzuki reaction has also been applied very successfully in the fields of polymer chemistry [525], as well as solid-phase chemistry and combinatorial library synthesis [526]. It has been applied industrially [527], especially in medicinal chemistry, for example, in the production of the antihypertensive drug losartan [224]. As described in Section 1.3.8.6, the use of masking groups allows iterative cross-couplings for a controlled synthesis of oligoarenes [427] and polyenes, including naturally occurring ones [426].

In the past decade alone, several new and further improved catalysts and ligands have been developed for difficult substrates such as aryl chlorides, which are cheaper and more available than bromides [528]. Among other advances, new phosphine-based systems developed by Fu [529], Buchwald [530], Organ [531], and others [532] even allow room-temperature couplings with aryl and heteroaryl chlorides. For example, Buchwald and coworkers developed a universal palladium catalyst system based on SPhos, a rationally designed ligand with unprecedented stability and scope for couplings of hindered aryl chlorides at room temperature (Equation 1.89) [533]. Organ and coworkers developed Pd-PEPPSI, a class of very active and broadly applicable palladium complexes of *N*-heterocyclic carbenes (NHC) (Equation 1.90) [531]. These and other phosphine-free systems based on NHC ligands were shown to perform very well even with hindered boronic acids and electrophiles [534]. Other transition metals were found to catalyze the reaction, notably nickel [535], ruthenium [536], iron [537], and gold [538], albeit the range of suitable substrates tends to be more limited. Interestingly, advantageous ligand-free [539] and even "palladium-free" couplings have even been reported [540]. Other classes of substrates such as polyfluoroarenes [541], aryltosylates [542], arylammonium salts [543], arylcarbamates and carbonates [225, 544], aryl methyl ethers [545], allylic halides and esters [546], and allylic ethers [547] were recently uncovered to further expand the scope of this cross-coupling chemistry. Allylic alcohols can couple directly with alkyl-, alkenyl-, and arylboronic acids [548]. Moreover, arylsulfonium salts [549], thioesters [550], and thioethers [551] were shown to be suitable electrophilic substrates. For example, heteroaromatic thioethers couple to arylboronic acids under base-free conditions promoted by copper(I) thiophene-2-carboxylate (Equation 1.91) [552]. A more detailed description of the Liebeskind–Srogl cross-coupling [553] can be found in Chapter 7. Likewise, more details and recent advances in the Suzuki–Miyaura cross-coupling reaction are described in detail in Chapter 4.

1.5.3.2 Transition Metal-Catalyzed Insertions, Cycloisomerizations, and C–H Functionalizations Based on Transmetalation of Boronic Acids

Numerous reaction processes have been reported based on exploiting the ability of boronic acids to transmetalate with Pd(II) and other transition metals, and a detailed overview would be beyond the scope of this chapter. Carbonylations and carboxylations of arylboronic esters to provide carboxyesters and acids are known (Equation 1.92, Figure 1.42) [554]. There are several examples of transition metal-catalyzed ring forming reactions employing boronic acids as electrophiles [555]. These processes are illustrated in a nice example by Murakami and coworkers of a palladium-catalyzed cyclization of 2-(alkynyl)aryl isocyanates terminated through a Pd(II) transmetalation/



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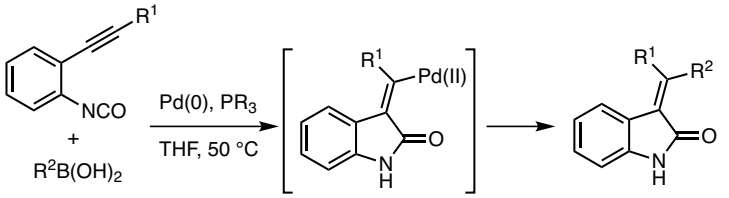

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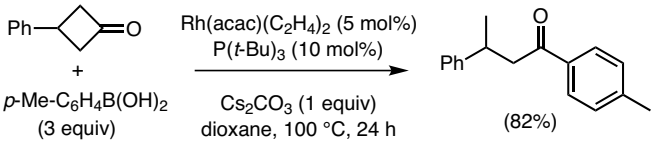

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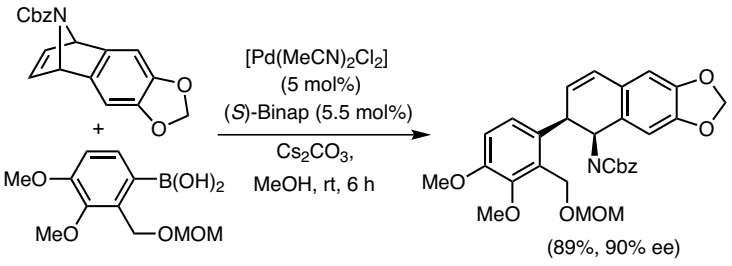

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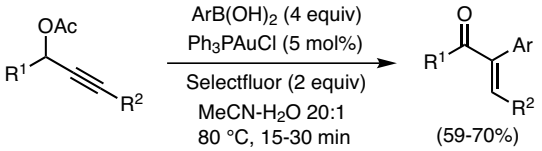

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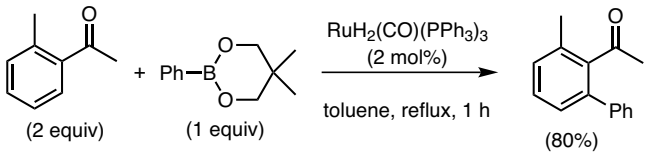

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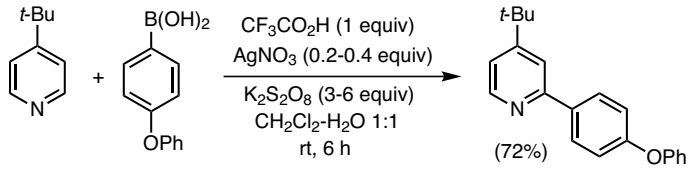

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Figure 1.42 Other transition metal-catalyzed transformations of boronic acids (esters).

reductive elimination (Equation 1.93) [556]. Cyclobutanones undergo a C–C bond insertion/functionalization with arylboronic acids (Equation 1.94) [557]. Other recent examples include the use of diazoesters as substrates, affording α,β-diaryl acrylates as products [558], copper-catalyzed stereospecific couplings between arylboronic acids and allylic phosphates [559], and a useful aromatic trifluoromethylation reaction [560]. A bicyclic allylic carbamate was opened enantioselectively in a key Pd(II)-catalyzed step toward the synthesis (+)-homochelidonine (Equation 1.95) [561]. Gold-catalyzed oxidative couplings using boronic acids were reported (Equation 1.96) [562]. Patel and Jamison reported a nickel-catalyzed three-component reaction between alkynes, imines, and organoboron compounds such as alkenyl- and arylboronic acids [563]. The resulting allylic amines are obtained in high regioselectivity. A palladium-catalyzed three-component reaction between allenes, organic halides, and boronic acids was reported [564].

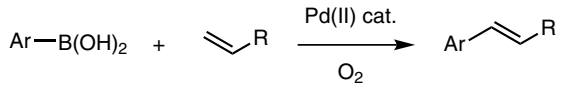
Recent interest in C–H activation/functionalization of arenes has motivated the use of boronic acids as partners. For example, arylboronic esters were used in a ruthenium-catalyzed *ortho*-arylation of aromatic ketones via C–H activation/functionalization (Equation 1.97) [565] or in a dealkoxylation/functionalization [566]. Several palladium-catalyzed variants using various directing groups [567], including functionalization of sp^3 centers [568], have been described recently using boronic acids to transmetalate with the Pd(II) intermediate of C–H activation. Silver-catalyzed α-arylation of pyridines (Equation 1.98) [569] and iron-mediated [570] direct arylations of unactivated arenes have also been reported.

1.5.3.3 Heck-Type Coupling to Alkenes and Alkynes

A number of reports have highlighted the ability of boronic acids to undergo rhodium- [571], ruthenium- [572], iridium- [573], or palladium(II)- [574] catalyzed addition–dehydrogenation reactions (oxidative Heck reaction) on alkenes (Equation 1.99, Figure 1.43). The Pd(II)-catalyzed variant is particularly versatile, as demonstrated with the assembly of [2]rotaxanes [575]. An interesting C-glycosylation of glycals provides different isomeric alkenes dependent on the choice of oxidant (Equation 1.100) [576]. A copper-catalyzed "Sonogashira-like" variant affords an aerobic oxidative addition between terminal alkynes and arylboronic acids that produce internal alkynes [577]. A rhodium-catalyzed addition onto 1-arylethenyl acetates affords stilbene derivatives via *cine* substitution [578].

1.5.3.4 Rhodium- and Other Transition Metal-Catalyzed Additions to Alkenes, Carbonyl Compounds, and Imine Derivatives

Another recent breakthrough in organoboron chemistry is the exciting discovery that rhodium(I) complexes catalyze the conjugate addition of boronic acids to carbonyl compounds [579] and a wide range of activated alkene substrates (Equations 1.101 and 1.102, Figure 1.44) [580]. The latter process, reviewed in Chapter 5, can even provide enantioselectivities over 99% with several classes of substrates [581]. Under certain conditions, diarylketones can be obtained in the Rh(I)-catalyzed addition of arylboronic acids to benzaldehydes [582]. A nickel–carbene catalyst was found effective directly from boronic esters under mild conditions [583]. Palladium



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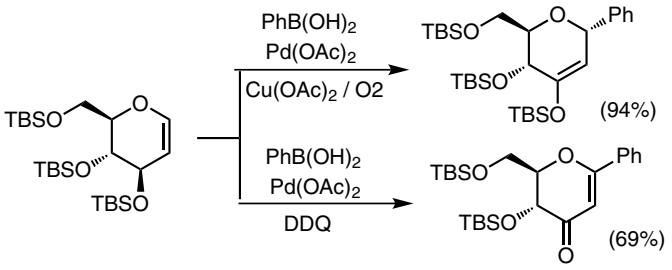

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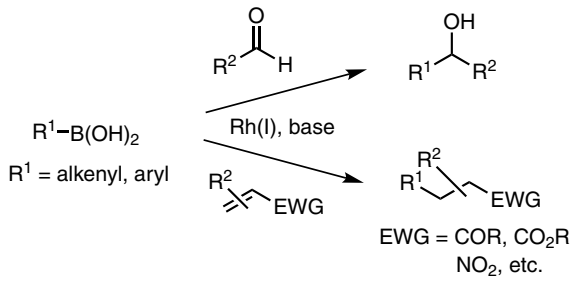
Figure 1.43 Heck-type reactions with boronic acids.

and nickel catalysts can also promote similar additions of boronic acids onto unactivated alkenes [584], alkynes (giving polysubstituted alkenes stereoselectively) [585], allenes [586], and 1,3-butadienes [587].

Selected recent examples of catalytic enantioselective additions of boronic acids and esters to aldehydes and ketones include rhodium- [588], copper- [589], and ruthenium-catalyzed methods (Equation 1.103) [590]. Rhodium-catalyzed additions to imine derivatives are possible [591]. For example, arylboroxines were shown to undergo a catalytic asymmetric addition to *N*-tosylarylimines [592]. This procedure



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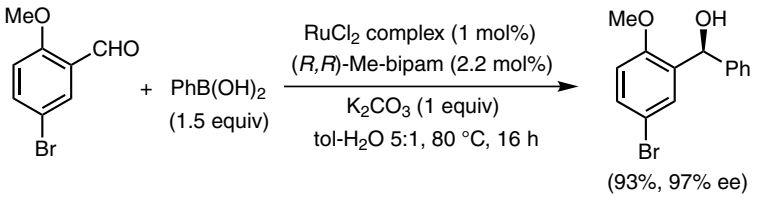

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Figure 1.44 Rhodium- and ruthenium-catalyzed additions of boronic acids onto carbonyl compounds and activated alkenes.

and other asymmetric variants provide branched amines with high stereoselectivities (see Chapter 9).

1.5.3.5 Diol-Catalyzed Additions of Boronic Esters to Unsaturated Carbonyl Compounds and Acetals

In addition to the above variant that makes use of transition metal catalysts, it was long known that strong Lewis acids can promote the conjugate addition of boronic esters to α,β-unsaturated carbonyl compounds [593]. More recently, it was shown that the B–C bond of alkynylboronic esters is labile enough to allow their uncatalyzed nucleophilic addition to enones, and a stoichiometric asymmetric procedure has been developed using binaphthyl alkynylboronates [594]. A catalytic variant employing chiral binaphthol catalysts was subsequently developed for both alkynyl- and alkenylboronates (Equation 1.104, Figure 1.45) [595]. The mechanism of these diol-catalyzed reactions has been debated to occur either through a simple transesterification (complete exchange to a more electrophilic arenediol ester) or via a mixed, Brønsted activated ester [596]. Using enals as substrates, secondary amine-catalyzed variants proceeding through iminium ion intermediates have been reported, albeit with limited scope and enantioselectivity [597]. Reagents other than allylic or propargylic boronates do not add spontaneously to carbonyl compounds. A recent report, however, describes enantioselective tartrate-derived diol-catalyzed additions of aryl- and alkenylboronates onto chromene acetals (Equation 1.105) [598].

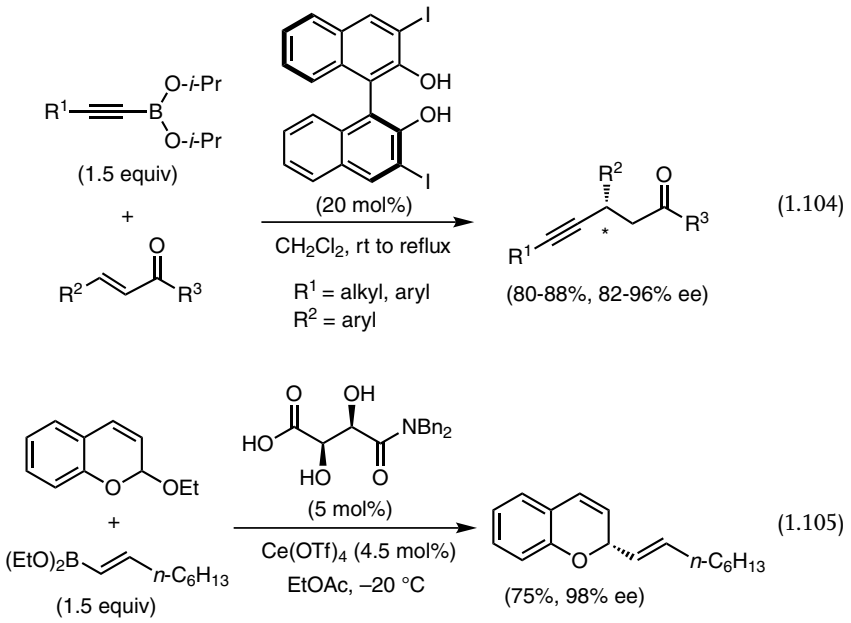


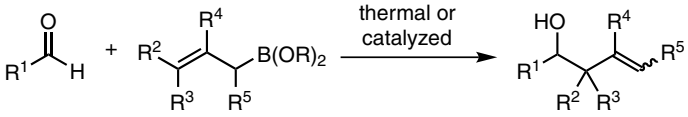
Figure 1.45 Diol-catalyzed additions of boronic esters.

1.5.3.6 Allylation of Carbonyl Compounds and Imine Derivatives

The uncatalyzed addition of allylic boronates to aldehydes was first disclosed in 1974 [599]. This reaction has since found tremendous use in the stereoselective synthesis of acetate and propionate units found in numerous natural products (Equation 1.106, Figure 1.46) [600]. One of the most recent developments of this reaction is the discovery that additions of allylboronates to aldehydes can be catalyzed by Lewis [601] and Brønsted acids [602]. The dramatic rate acceleration observed in these variants allows a substantial decrease in the reaction temperature, which in turn leads to outstanding levels of diastereo- and enantioselectivity using chiral catalysts [603]. Since then, many newer catalytic procedures for additions of allylic boronates to carbonyl compounds and imine derivatives have been developed, as well as efficient methods for the preparation of functionalized reagents [600]. Many of these advances are described in Chapter 8.

1.5.3.7 Uncatalyzed Additions of Boronic Acids to Imines and Iminiums

In 1993, Petasis disclosed a novel Mannich-type multicomponent reaction between alkenylboronic acids, secondary amines, and paraformaldehyde [604]. Subsequently, a variant between α-ketoacids, amines, and boronic acids was developed, providing a novel synthetic route to α-amino acids (Equation 1.107, Figure 1.46) [605a]. The use of α-hydroxyaldehydes lends access to β-amino alcohols in high yields and stereoselectivity (Equation 1.108) [605b], and both alkenyl- and arylboronic acids can be employed. A catalytic asymmetric approach has been reported in 2008 [606]. The Petasis borono-Mannich reaction was reviewed recently [607], and its mechanism and applications are discussed with several examples in Chapter 9.



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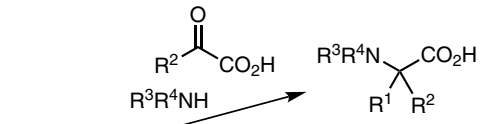

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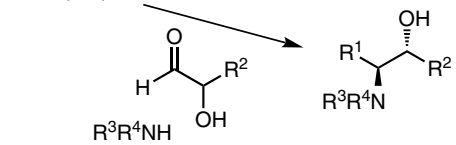

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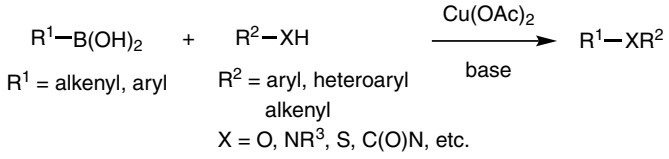
Figure 1.46 Other C–C bond forming reactions of boronic acids (esters): carbonyl allylboration and Petasis borono-Mannich reaction.



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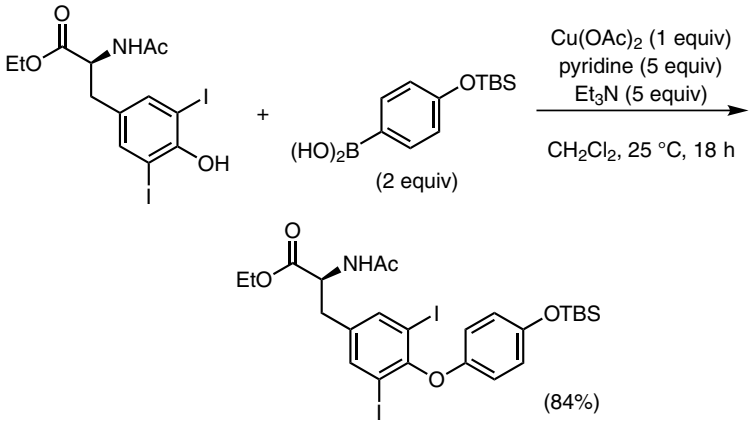


(1.110)

Figure 1.47 Copper-catalyzed coupling of boronic acids with oxygen and nitrogen compounds.

1.5.4 Carbon–Heteroatom Bond Forming Processes

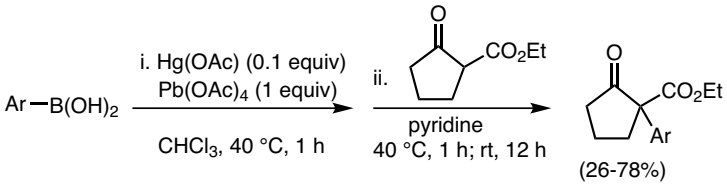
1.5.4.1 Copper-Catalyzed Coupling with Nucleophilic Oxygen and Nitrogen Compounds

In 1998, groups led by Chan, Evans, and Lam independently reported their observation that copper diacetate promotes the coupling of aryl and heteroaryl boronic acids to moderately acidic heteroatom-containing functionalities like phenols, thiols, amines, amides, and various heterocycles (Equation 1.109, Figure 1.47) [608–610]. The potential of this mild and general method was convincingly exemplified with the syntheses of the diaryl ether units of a thyroxine intermediate (Equation 1.110) [609] and the teicoplanin aglycon related to vancomycin [211]. This new reaction has since been extended to other classes of substrates, including applications in solid-phase synthesis [611]. A mechanism was suggested based on transmetalation of the boronic acid with $Cu(OAc)_2$, followed by ligand exchange with the nucleophilic substrate, and reductive elimination to give the coupling product [608]. These copper-catalyzed heterocoupling reactions of boronic acids constitute the main topic of Chapter 6.

1.5.5 Other Reactions

1,3-Dicarbonyl compounds are arylated with arylboronic acids in the presence of lead tetraacetate and catalytic $Hg(OAc)_2$ under *in situ* conditions that promote a rapid

boron–to–lead transmetalation (Equation 1.111, Figure 1.48) [612]. A more recent method for α-arylation and α-vinylation of carbonyl compounds consists in adding boroxines to α-diazocarbonyl compounds via palladium catalysis [613a] or thermal, base-promoted catalysis (Equation 1.112) [613b]. A similar, metal-free reductive



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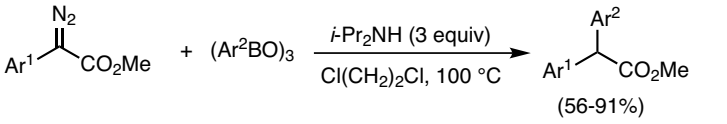

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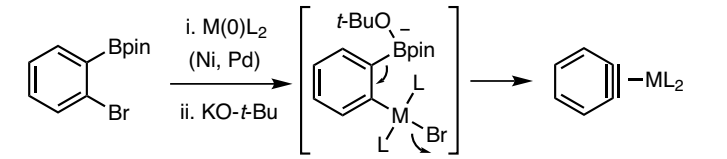

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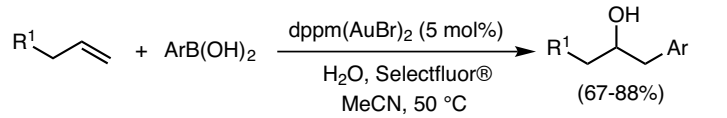

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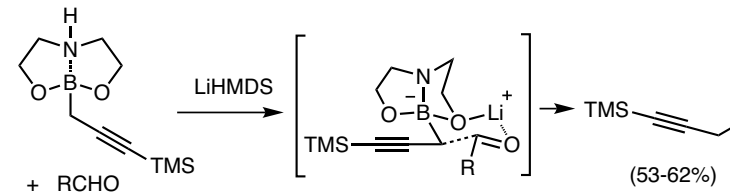

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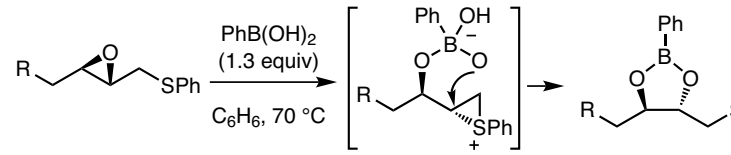

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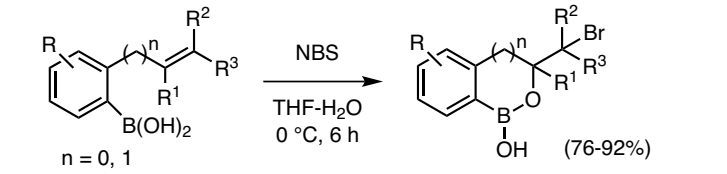

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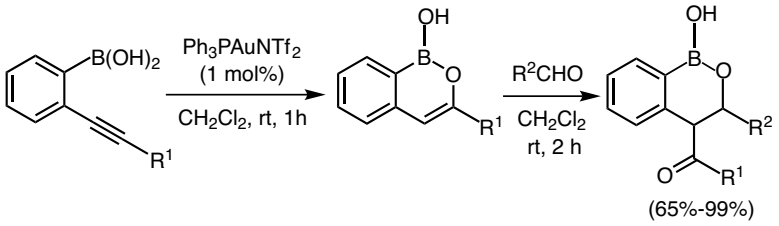
Figure 1.48 Selected examples of miscellaneous reactions of boronic acid derivatives.



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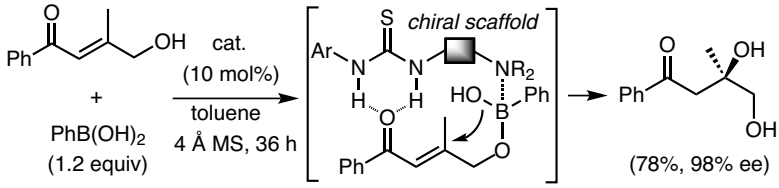


(1.119)

Figure 1.48 (*Continued*)

coupling between tosylhydrazones and arylboronic acids was recently described [614]. Allylic carbonates [615] and even amines [616] provide cross-coupling products with boronic acids under nickel catalysis. The metalation of *ortho*-bromobenzeneboronic esters was shown to be an effective route to benzyne complexes of Group 10 metals (e.g., Ni, Pd) (Equation 1.113) [617]. Boronic acids have been employed in multicomponent reaction processes other than the Petasis reaction (Section 1.5.3.7). They were shown to react with diazocyclopentadiene and rhenium(I) tricarbonyl complex to give new monoalkylated cyclopentadienyl rhenium complexes [618]. Recently, fluoride-enabled cationic gold-catalyzed processes were reported that employ boronic acids as reagents. An interesting three-component oxidative alkoxy- and hydroxyarylation of alkenes was described (Equation 1.114) [619], purportedly via Au(III) activation of the alkene pi-bond, and a related hydration/functionalization of alkynes was reported [620]. A chemo- and regioselective Ru(II)-catalyzed cyclotrimerization involving alkynylboronates and two other alkynes can be turned into a four-component synthesis of polysubstituted arenes when combined with a one-pot Suzuki coupling [262a]. A stereoselective three-component reaction between zincated hydrazones, alkenylboronates, and electrophiles was described [621].

Diethylzinc can promote a B–Zn transmetalation of organoboronates followed by a Lewis acid-catalyzed asymmetric 1,2-addition to aldehydes or ketones [457]. Recently, it was found that diethanolamine propargyl boronates can be activated by a strong base and can undergo α-addition to aldehydes (Equation 1.115) [622]. This unique behavior contrasts with the traditional use of allylic and propargylic boronic esters, which add at the γ-carbon. Although nickel- [535] and iron- [537] catalyzed couplings are thought to involve radical intermediates, another uncommon role for boronic acids is their use as precursors of radicals. Exceptionally, radical cyclizations that are initiated by treatment of 2-arylboronic acids with manganese triacetate were recently reported [623].

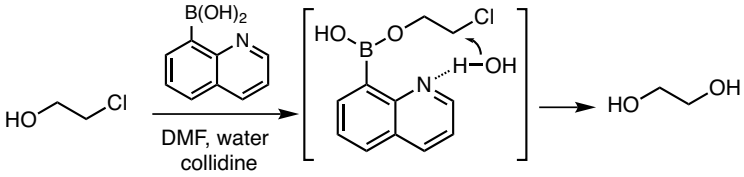
Under favorable conditions, the hydroxyl group of boronic acids can serve as an internal nucleophile. For example, epoxy sulfides are opened stereoselectively by phenylboronic acid to afford diol products (Equation 1.116) [624]. A variant of this process makes use of a palladium catalyst [625]. Boronic acids have been employed as internal nucleophiles in a bromo-boronolactonization of olefins (Equation 1.117) [626]. Recently, Au(I) catalysis was applied to similar substrates, giving transient boron enolates that can be further reacted with aldehydes (Equation 1.118) [627]. Falck and coworkers developed an ingenious chiral amine-catalyzed, boronic acid-promoted oxy-Michael reaction (Equation 1.119) [628].

1.6
Overview of Other Applications of Boronic Acid Derivatives

1.6.1
Use as Reaction Promoters and Catalysts

By forming transient esters with alcohols, boronic acids have the capability to act as catalysts or templates for directed reactions [629]. In the early 1960s, Letsinger demonstrated that a bifunctional boronic acid, 8-quinolineboronic acid, accelerates the hydrolysis of certain chloroalkanols (Equation 1.120, Figure 1.49) [630], and that boronoarylbenzimidazole serves as catalyst for the etherification of chloroethanol [631]. Mechanisms involving covalent hemiester formation between the boronic acid in the catalyst and the alcohol substrate, combined with a basic or nucleophilic participation of the nitrogen, were invoked. Yamamoto and coworkers found that a number of electron-poor arylboronic acids, in particular 3,4,5-trifluorobenzeneboronic acid, catalyze the direct amidation reactions between carboxylic acids and amines [632]. Hall and coworkers recently identified improved catalysts such as *ortho*-iodobenzeneboronic acid, which functions at room temperature to give high yields of amides from aliphatic amines and acids (Equation 1.121) [633]. Arylboronic acids can also catalyze aldol reactions [634], various cycloadditions of α,β-unsaturated caboxylic acids [635], Friedel–Crafts alkylation of benzylic alcohols (Equation 1.122) [636], and transpositions of allylic and propargylic alcohols [637]. Arylboronic acids can also catalyze the hydrolysis of salycylaldehyde imines [638] and affect the alkaline conversion of D-glucose into D-fructose [639]. Phenylboronic acid assists in the cyclodimerization of D-glucosamine into a pyrazine [640] and in the photocyclization of benzoin into 9,10-phenanthrenequinone [641].

Boronic acids can be employed to promote templating effects. Narasaka *et al.* demonstrated that phenylboronic acid can be employed to hold a diene and dienophile in such a way that the regiocontrol of a Diels–Alder reaction can even be inverted [642]. This templating strategy was elegantly exploited in the synthesis of a key intermediate in the total synthesis of taxol by Nicolaou *et al.* (Equation 1.123) [643]. By using a similar effect, phenols are *ortho*-alkylated with aldehydes through a proposed six-membered transition state where phenylboronic acid, used stoichiometrically, holds the two reactants in place (Equation 1.124) [644].



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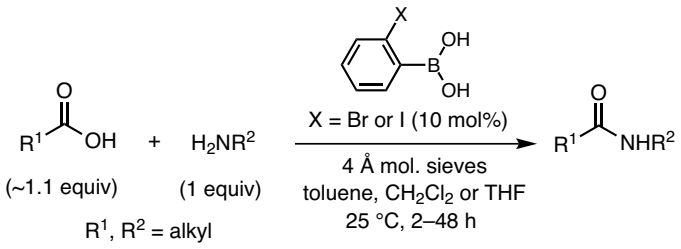

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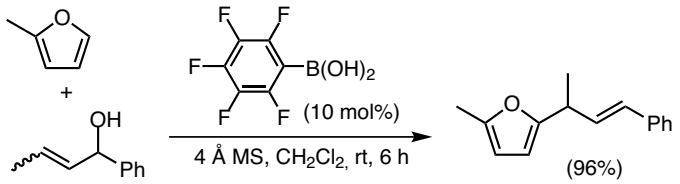

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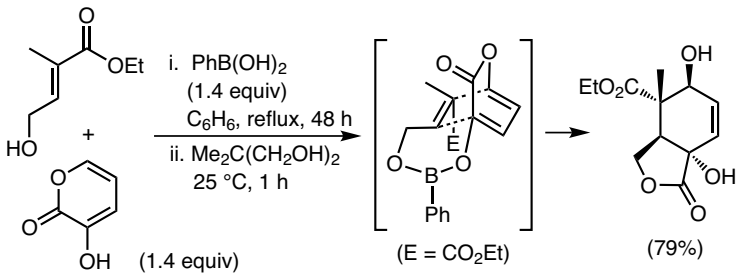

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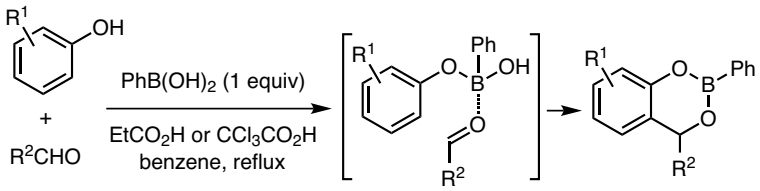

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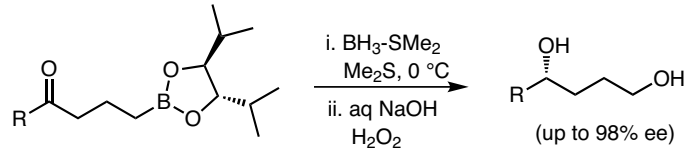

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Figure 1.49 Selected examples of applications of boronic acids (esters) as reaction promoters and catalysts.

Molander *et al.* have demonstrated the existence of neighboring group participation from a chiral boronate in the reduction of ketones (Equation 1.125) [645]. A highly ordered cyclic transition structure with boron–carbonyl coordination was invoked to explain the high level of remote stereoinduction. The reduction of imine derivatives was also performed with high selectivity [646].

Boronic acids and their derivatives are very popular as components of chiral Lewis acids and promoters for a variety of reaction processes [629]. Indeed, chiral acyloxyboranes and the oxazaborolidines (Section 1.2.3.6) and their protonated salts made a mark in organic synthesis [180–182]. A tartramide-derived dioxaborolane is a key chiral promoter in the asymmetric cyclopropanation of allylic alcohols [647]. More examples and details on the applications of boronic acid derivatives as reaction promoters and catalysts are provided in Chapter 12.

1.6.2
Use as Protecting Groups for Diols and Diamines

The use of boronic acids to protect diol units in carbohydrate chemistry has been demonstrated several decades ago, in particular by the work of Ferrier [648] and Köster [649]. For example, whereas an excess of ethylboronic acid (as the boroxine) leads to a bisboronate furanose derivative of D-lyxose, equimolar amounts provided 2,3-*O*-ethylboranediyl-D-lyxofuranose (Equation 1.126, Figure 1.50) [650]. From the latter, a regioselective diacetylation reaction followed by treatment with HBr led to the desired α-D-lyxofuranosyl bromide in very high yield. An alternative method for the preparation of cyclic alkylboronic esters involves treatment of diols with lithium trialkylborohydrides [105]. Phenylboronic esters of carbohydrates have also been exploited in the regioselective sulfation of saccharides [651], and as a way to regioselectively alkylate diol units of pyranosides [652]. The reaction of phenylboronic acids with nucleosides and mononucleotides was described long ago [653]. The *ortho*-acetamidophenyl boronate group was employed to protect the vicinal 1,2-diol of adenosine [395]. It was found more resistant to hydrolysis than the corresponding phenylboronate, which was ascribed by the authors to the beneficial coordination effect of the *ortho*-substituent. Phenylboronic acid has also been used as a protecting group for 1,2- and 1,3-diol units of other natural products such as terpenes [654], macrolides [655], prostaglandins [656], quinic acid derivatives [657], anthracyclines [658], steroids [659], macrocyclic polyamines [660], and polyether antibiotics [661]. Typically, phenylboronates are made by a simple condensation with a diol, which can be eventually deprotected by exchange with another diol or by a destructive oxidation with hydrogen peroxide. For example, phenylboronic acid was employed to selectively protect the 1,3-diol unit of a triol (Equation 1.127, Figure 1.50) [661]. Oxidation of the remaining hydroxyl and oxidative deprotection of the phenylboronate led to a concomitant cyclization to give a pyran product. A high-yielding solid-state method for the protection of diols, polyols, and diamines with $PhB(OH)_2$ was described [662]. Phenylboronic acid was also employed as an *in situ* protective reagent in osmium tetraoxide-promoted dihydroxylation of alkenes [663]. In this variant, it serves as a water replacement for cleavage of the osmate intermediate while

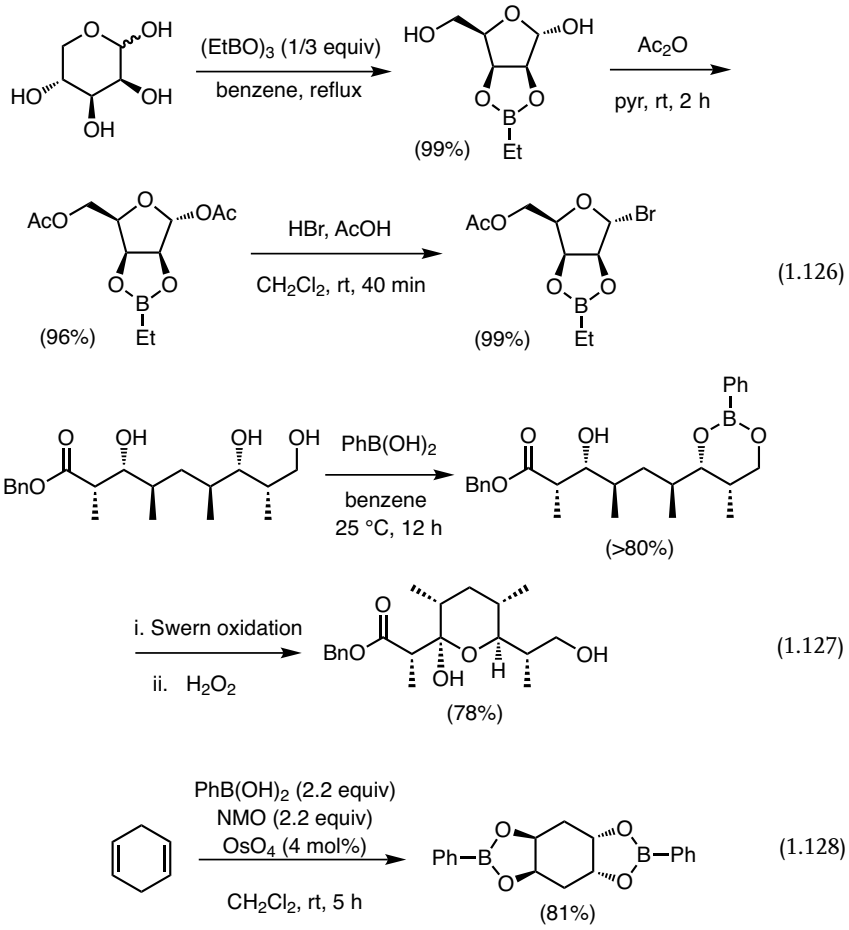


Figure 1.50 Examples of the use of boronic acids for the protection of diol compounds.

providing a nonpolar cyclic boronate derivative that is easier to extract in organic solvents compared to the free diol. Sharpless and coworkers applied this "boronate capture" procedure to the dihydroxylation of polyenes (Equation 1.128) and found several further advantages such as faster reaction times, minimization of over-oxidation, and a marked effect on the diastereoselectivity of these multiple dihydroxylations [664].

1.6.3
Use as Supports for Immobilization, Derivatization, Affinity Purification, Analysis of Diols, Sugars, and Glycosylated Proteins and Cells

The concept of immobilizing or enriching diol compounds with a boronic acid-conjugated support as a sort of heterogeneous protecting group strategy is the

antipode of the diol-based supports described in Section 1.4.2. Examples of such boronic acid matrices include polystyryl boronic acid resins (**119**) [665–667], the cellulose-derived support **120** [668], the methacrylic polymer **121** [669], and the polyacrylamide-supported nitroarylbenzene boronic acid **122** [670] (Figure 1.51). Recently, nanoparticles [671] and modified silica [672] have received significant attention. The applications of immobilized boronic acids have been reviewed and include the purification or analysis of carbohydrates and glycopeptides, diverse nucleic acid derivatives embedding rigid vicinal *cis*-diols, and catechols including L-DOPA, catechol estrogens, and catecholamines from urine [673, 674]. For instance, one of the most important biomedical uses of immobilized boronic acids is in the enrichment and quantification of glycosylated peptides and proteins [675], such as the level of glycosylated hemoglobin in red blood cells, which is an important indicator for the clinical analysis of diabetes. Boronic acid-functionalized composite nanoparticles were used to enrich glycoproteins from human colorectal cancer tissues to identify

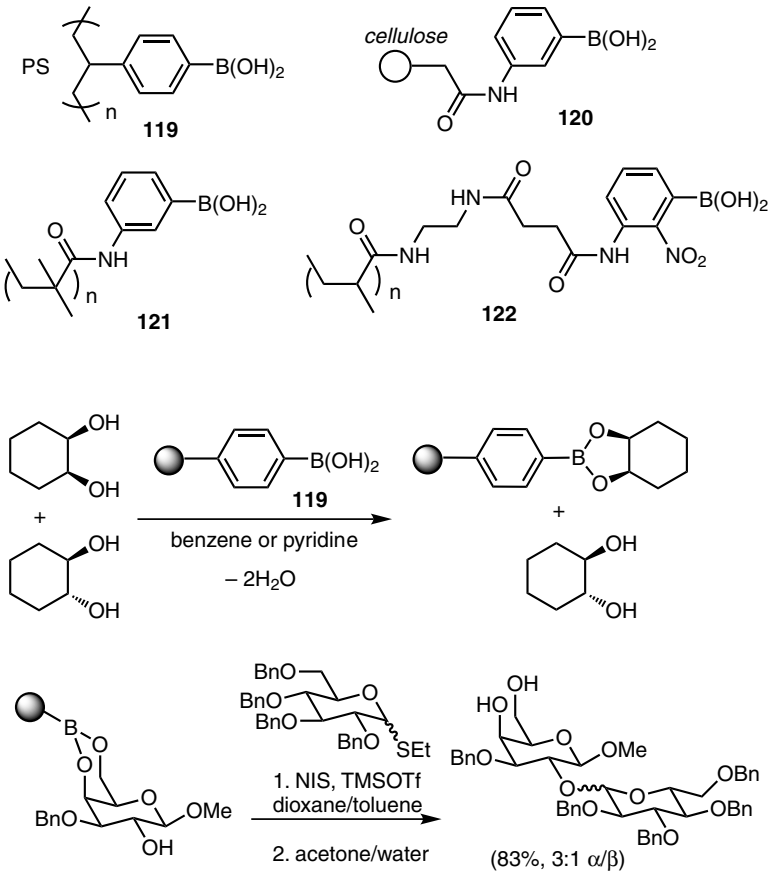


Figure 1.51 Boronic acid supports for diol compounds.

N-glycosylation sites [671a] and to analyze diol-containing antibiotics in milk samples [671b]. In one other application, a water-soluble polyacrylamide copolymer was tested as a mitogen for lymphocytes [676]. Other supports have also been considered as components of sensing systems for glucose [677–679] and nucleotides such as AMP [680]. With hydrogels, the extent of carbohydrate binding can be correlated with swelling (change in volume) [679]. All of the above arylboronic acid supports demonstrate a selectivity profile similar to their homogeneous counterpart, and only *cis*-diols of a favorable coplanar geometry can be immobilized efficiently. For example, polystyryl boronic acid (**119**) was put to use in the fractionation of carbohydrates and in the separation of isomeric diols [665, 681]. In agreement with the stereochemical arguments discussed in previous sections, of the *cis*- and *trans*-1,2-cyclohexenadiol isomeric mixtures, only the former bound to resin **119**, thereby allowing an effective separation of the two isomers (Equation 1.129, Figure 1.51) [681]. The boronic acid-substituted methacrylic polymer **121** was employed to separate ribonucleosides and deoxyribonucleoside mixtures [669]. The selectivity profile of support **120** in the binding of various nucleic acid and sugar derivatives was studied. Not surprisingly, the heterogeneous boronate formation process in a chromatography column was found to be more efficient at a higher pH, with diols of favorable geometry, and also dependent on the ionic strength and the nature of the cations in the eluent [668]. A Wulff-type (cf. Section 1.2.2.4.1) amino-boronic acid-functionalized copolymeric monolith, however, was claimed to bind diol-containing biomolecules as neutral pH [682]. Polyacrylamide support **122** was employed in the purification of transfer ribonucleic acids [670]. Due to the low pK_a (about 7) of its electron-poor boronic acid unit, the immobilization process was performed efficiently at neutral pH, and recovery of the tRNA from the column occurred at pH 4.5. In hopes of further increasing affinity and selectivity in carbohydrate binding, the technique of molecular imprinting polymerization was tested with boronic acid-containing monomers [66a, 683, 684].

Fréchet also demonstrated the utility of resin **119** in the selective immobilization and transformation of carbohydrate derivatives [666a, 685]. Inspired by this work, Boons and coworkers used the same resin as a reusable linker system for the solid-phase synthesis of oligosaccharides (Equation 1.130, Figure 1.51) [686]. In exciting recent applications, boronic acid-functionalized surfaces were employed in the preparation of microarrays of carbohydrates [687], Fc-fused lectins [688], and the electrochemically addressable immobilization of cells [689].

1.6.4
Use as Receptors and Sensors for Carbohydrates and Other Small Molecules

The ability of boronic acids to form esters reversibly with *cis*-diols (Section 1.2.3.2.3) has been a central theme in the intensive area of sensor and receptor development for oligosaccharides. This very active research area has been reviewed regularly [674, 690], including the previous edition of this monograph. These molecules can be used

for a variety of applications such as derivatizing agents for the chromatographic detection of carbohydrates, and in particular in the important social health issue of blood glucose monitoring for diabetes patients. A two-component system based on boronic acid-appended viologen dyes is making significant progress toward this application [691]. Progress has also been made in the development of selective receptors for complex oligosaccharides [692] and glycoproteins [693]. Some of these most recent advances in the field of carbohydrate sensing and recognition with boronic acids are reviewed in Chapter 13.

Mixed receptors containing boronic acids and charged functionalities were also developed for the recognition of sugar acids [694] and even for heparin [394], a polysulfated saccharide. Boronic acid sensors can also target catechols like L-DOPA and dopamine [695], catecholamines in urea [696], polyphenols in green tea [697], α-hydroxycarboxylic acids [698], and receptors selective for tartrate were reported [699].

1.6.5
Use as Antimicrobial Agents and Enzyme Inhibitors

Although there has been significant activity in the area of boron therapeutics over the past decade [700]. Michaelis and Becker first noted the toxicity of phenylboronic acid against microorganisms and its relative harmlessness against higher animals more than a century ago [228]. The antimicrobial properties of simple arylboronic acid derivatives have been further examined in the 1930s [202]. Interestingly, the activity of arylboronic acids in plants has been investigated thoroughly, and several of them were found to promote root growth [60, 62]. Several boronic acids and their benzodiaza- and benzodioxaborole derivatives were evaluated as sterilants of houseflies [61]. A number of boronic acids and esters display potent antifungal activity [701]. For instance, the diazaborine family, exemplified by the thienodiazaborine **123** (Figure 1.52), has long been known to possess potent activity against a wide range of Gram-negative bacteria [702] by targeting the NAD(P)H-dependent enoyl acyl carrier protein reductase [703]. This enzyme is involved in the last reductive step of fatty acid synthase in bacteria, and the structure of the inhibitory complex with diazaborines in the presence of the nucleotide cofactor was elucidated by X-ray crystallography [704]. Interestingly, the bisubstrate complex shows a covalent bond between boron, in a tetracoordinate geometry, and the 2′-hydroxyl of the nicotinamide ribose. In addition to their potential in the fight against microbial resistance in *Mycobacterium tuberculosis* and other strains, diazaborine compounds may find other medicinal applications as estrogen mimics [705]. A prostaglandin mimetic where a boronyl group replaces the carboxylate, **124**, was found to be moderately active [706]. Other boronic acid compounds have been identified as inhibitors of β-lactamase [707], histone deacetylase [708], tubulin polymerization [709], and carboxypeptidase [710], among others. The cyclic hemiboronic ester 4-fluorobenzoxaborole, **125**, was found to inhibit the terminal nucleotide in the editing site of the tRNA-isoleucyl synthetase complex, **126**, by forming a hydrogen-bonded boronate

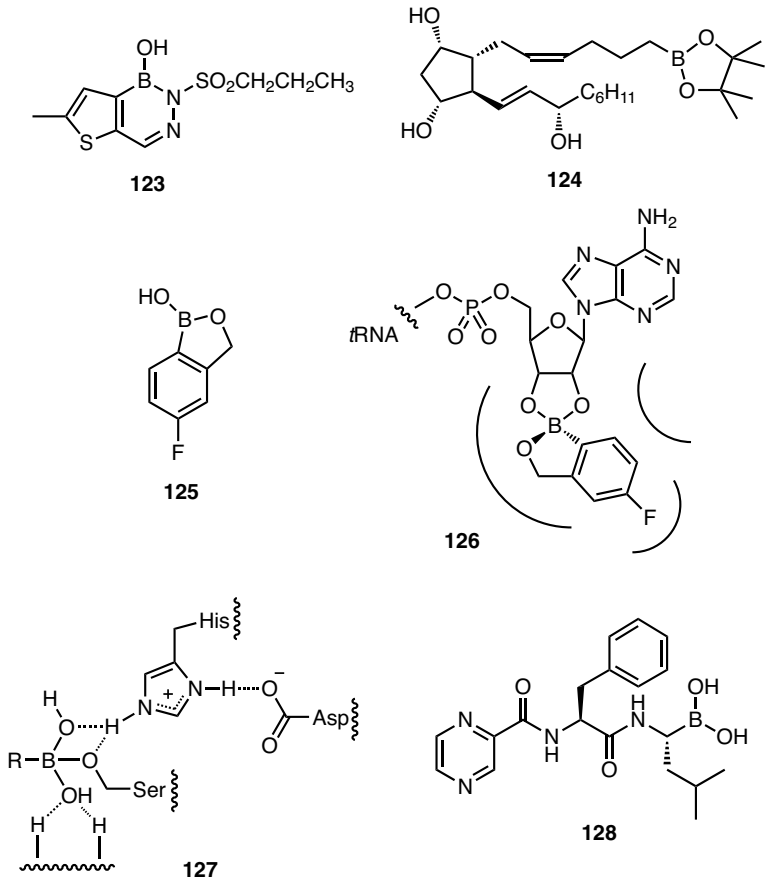


Figure 1.52 Examples of biologically active boronic acids. *Note*: Compound **128** is the dipeptidyl boronic acid antineoplastic drug bortezomib, a proteasome inhibitor.

(Figure 1.52) [711]. This antifungal compound is currently entering phase 3 clinical studies for the treatment of onychomysis. Related compounds with this new boron pharmacophore have been recently reported [712]. A multivalent boroxole-functionalized polymer shows potential as a vaginal microbicide targeting the pg120 HIV viral envelope, with minimal cytotoxicity to human cells [713].

Boronic acids have long been known to inhibit hydrolytic enzymes such as serine proteases [700], and the efficiency of a sepharose-based arylboronic acid sorbent in the chromatographic purification of this class of enzymes has been demonstrated [714]. In the development of boronic acid-based enzyme inhibitors as pharmaceutical drugs, target specificity within a wide family is crucial in order to avoid side effects. The development of the α-aminoalkylboronic acid analogues of α-amino acids was key in the recent development of potent peptidylboronic acid analogues with improved specificity. The usual mechanism of inhibition is believed to be the

formation of a tetracoordinate boronate complex (**127**, Figure 1.52) with the side chain hydroxyl nucleophile of the active serine residue, thus mimicking the tetrahedral intermediate for amidolysis [715]. Other modes of inhibition have been identified, however, involving formation of covalent adducts with the serine or histine residues of the active site [716, 717]. The validity of this concept was confirmed with the commercialization of the peptidylboronic acid antineoplastic drug bortezomib, Velcade™ (**128**), for the treatment of relapsed and refractory multiple myeloma [718, 719]. Bortezomib is the first boronic acid drug on the market. This discovery and other recent efforts in the medicinal chemistry of boronic acids are described in Chapter 13.

1.6.6
Use in Neutron Capture Therapy for Cancer

Several boronic acids such as 4-boronophenylalanine (**68**, Figure 1.17) have been evaluated as boron carriers for their potential use in a form of therapy for malignant brain tumors and other locally advanced cancers (head, neck) based on the technology of soft neutron capture [720]. Although this technology is making steady progress, it is still in experimental stage, giving promising outcomes in a few reported cases [721]. The selective delivery of sufficient concentrations of boron to the tumor site is a major issue for success [722].

1.6.7
Use in Transmembrane Transport

As first demonstrated with monosaccharides by Shinbo *et al.*, the ability of boronic acids to complex diols can be exploited in the study of molecular transport across lipophilic membranes [723]. Compounds that possess such carrier properties have potential applications in drug delivery. For example, Mohler and Czarnik demonstrated the ability of a cholanyl 3-pyridiniumboronic acid derivative (**129**, Figure 1.53) to transport ribonucleosides across a dichloroethane liquid membrane [724]. Other examples of boronic acid-based systems include a three-component amino acid transport system [725], the cathecholamine transporter **130** [726], and various carriers for monosaccharides such as fructose [59]. In fact, one of the most important potential applications of boronic acid carriers is in the area of development of selective fructose-permeable liquid membranes [727]. D-Fructose is the sweetest and most valuable of all common natural sweeteners. Its current production as a "high-fructose corn syrup," enriched from crudes containing other sugars, is an energy-intensive industrial process involving the evaporation of large quantities of water. The use of membrane-based technology could be highly advantageous due to its potential amenability to a continuous automated process. Detailed reviews on the use of boronic acids in membrane transport last appeared in 2004 [728]. Recent advances include the use of lipophilic Wulff-type 2-(aminomethyl) phenylboronic acid [729] and the use of boronic acid **131** (Figure 1.53) for target-selective, controllable vesicle membrane fusion as demonstrated with inositol triggering [730].

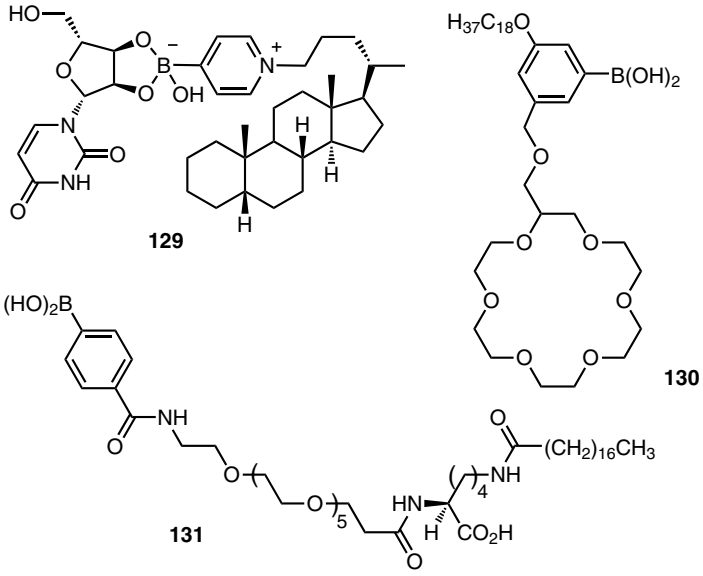
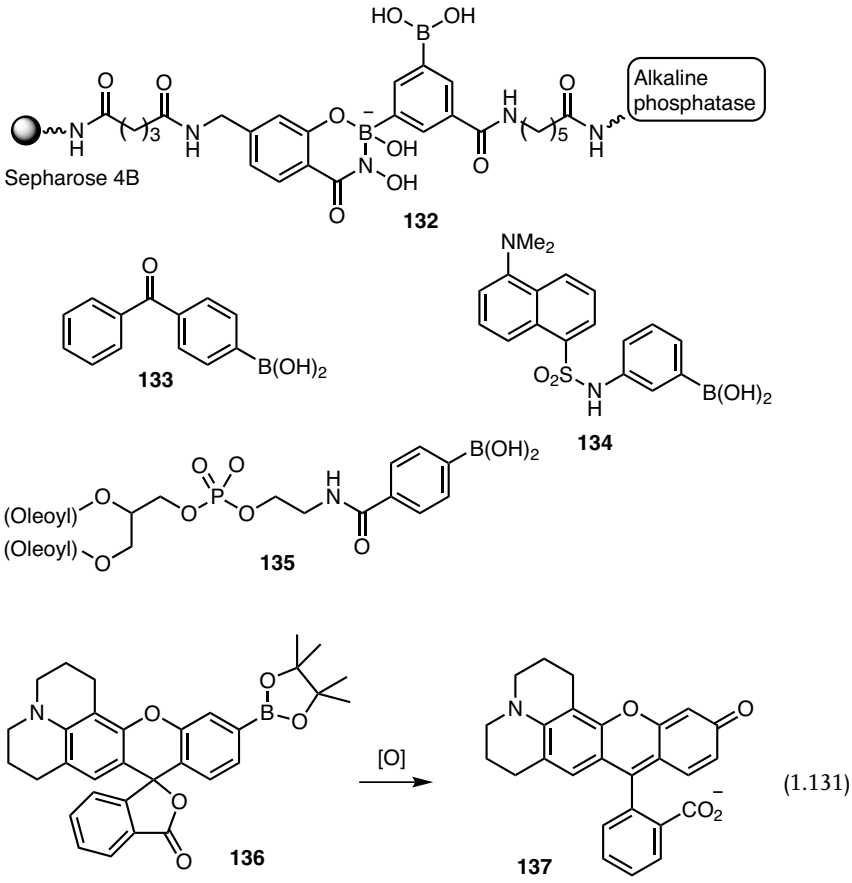


Figure 1.53 Examples of boronic acid-based transporters.

1.6.8
Use in Bioconjugation and Labeling of Proteins and Cell Surface

Proteins and enzymes can be linked covalently to 3-aminophenyl boronic acid, and the resulting conjugates were shown to bind to small *cis*-diol molecules and glycated hemoglobin [731]. Studies both in solution and using gel chromatography confirmed the low affinity of the boronate interaction. To address this problem, a conjugation method was developed based on the relatively stronger salicylhydroxamic acid–boronate interaction [177, 732]. As demonstrated on a diboronic acid–alkaline phosphatase conjugate **132** (Figure 1.54), higher affinity over a wider range of pH can be achieved by taking advantage of polyvalent interactions with the complexing sepharose support. An elegant and more contemporary approach to the fluorescent labeling of proteins was disclosed whereby an optimal tetraserine (tetraol) peptide sequence expressed on a protein terminal recognizes a diboronic acid dye with submicromolar affinity (Chapter 13) [733]. An alternative approach to covalent labeling employs an iodoaryl-modified mutant protein that can undergo Suzuki–Miyaura cross-coupling with a boronic acid "label" under physiological conditions [734].

A benzophenone boronic acid, **133** (Figure 1.54), was employed for probing altered specificity of chemically modified mutant subtilisin enzymes by photoaffinity labeling [735]. As discussed in Section 1.6.3, boronic acid supports can be employed to purify glycohemoglobin. A related soluble and colored arylboronic acid was reported for the quantification of these proteins [736]. More than three decades ago, a dansyl-labeled arylboronic acid (**134**) was reported to bind to the cell wall of the bacteria *Bacillus subtilis* presumably via boronate ester formation with the sugar



(1.131)

Figure 1.54 Boronic acid compounds used in protein labeling and conjugation, and as probes in chemical biology.

coating [737]. In the same study, a diboronic acid was found to agglutinate erythrocytes. Smith and coworkers designed liposomes containing a phospholipid bearing an arylboronic acid (e.g., **135**), and demonstrated the binding of these liposomes to erythrocytes presumably through interaction with the glycocalyx [738]. A specific diboronic acid sensor was shown to bind to tumor cells overexpressing the fucosylated sialyl Lewis X trisaccharide (Chapter 13) [739].

1.6.9
Use in Chemical Biology

There has been increasing interest in the use of boronic acids as probes to study cell biology and as components of synthetic proteins. For example, Chang and coworkers developed several fluorescent polyarylboronic acid dyes of various emission colors as *in vivo* indicators of reactive oxygen species such as hydrogen peroxide [740, 741].

For example, peroxyoorange 1 (**136**) turns to its quinone-phenolic form **137** upon exposure to peroxide, as demonstrated in macrophages (Equation 1.131, Figure 1.54) [741]. Catalytic antibodies with amide hydrolase activity were generated using a boronic acid hapten based on the concept of protease inhibition described in Section 1.6.5 [742]. More recently, unnatural amino acid mutagenesis was utilized to site-selectively insert 4-boronophenylalanine as a "genetically encoded chemical warhead," and the resulting proteins were shown to bind to an acyclic aglycon [743]. Hoeg-Jensen *et al.* designed a new concept for peptide or protein protraction by soluble reversible self-assembly based on boronic acid–diol interactions. This concept was demonstrated with hexameric insulin, which could be disassembled and released by addition of sorbitol or glucose [744]. More details on the applications of boronic acids in chemical biology can be found in Chapter 13.

1.6.10
Use in Materials Science and Self-Assembly

One of the major new directions in the application of boronic acids is their use as building blocks in the design and preparation of new materials [745] and in self-assembly [746] (e.g., Figure 1.14). For example, the formation of rigid oligomeric boronic anhydrides led to the preparation of a new class of covalent organic frameworks such as the crystalline porous solid COF-1 (**138**, Figure 1.55) [100]. COF-1 demonstrates high surface area and is thermally stable up to 500 °C. Many other bonding modes of boronic acids can be exploited in the design of new materials, such as hydrogen bonding dimerization (as in Figure 1.3b), boronic ester formation, Lewis base coordination, and even mixed bonding modes involving reversible covalent interactions with appended aldehydes, amines, and amino and other functionalities.

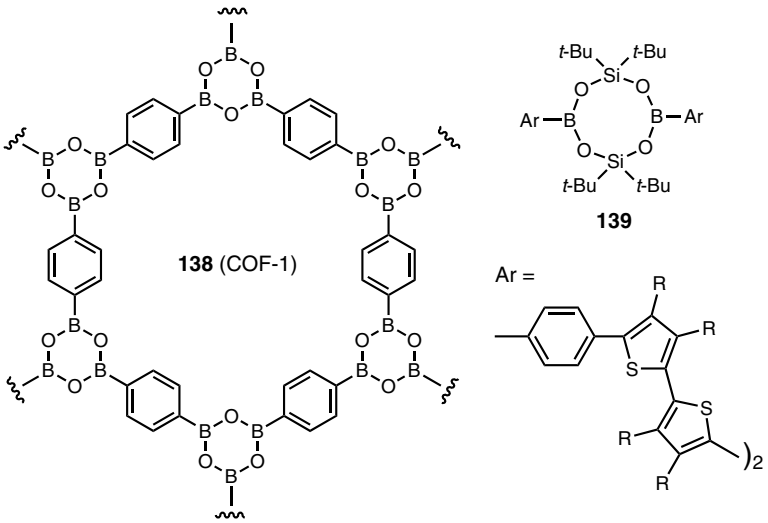


Figure 1.55 Examples of functional materials based on boronic acid components.

For example, mixed boronic siloxanes of type **139** were developed as conjugated polymer sensors [747]. Existing polyol materials such as lignin may be modified with boronic acids [748]. More applications of boronic acids in materials science are described in detail in Chapter 14.

References

1 (a) Frankland, E. and Duppa, B.F. (1860) *Justus Liebigs Ann. Chem.*, **115**, 319; (b) Frankland, E. and Duppa, B. (1860) *Proc. R. Soc. Lond.*, **10**, 568; (c) Frankland, E. (1862) *J. Chem. Soc.*, **15**, 363.

2 Brown, H.C. (1975) *Organic Synthesis via Boranes*, John Wiley & Sons, Inc., New York.

3 Matteson, D.S. (1995) *Stereodirected Synthesis with Organoboranes*, Springer, Berlin.

4 Lappert, M.F. (1956) *Chem. Rev.*, **56**, 959–1064.

5 Pelter, A., Smith, K., and Brown, H.C. (1988) *Borane Reagents*, Academic Press, New York.

6 Mikhailov, B.M. and Bubnov, Y.N. (1984) *Organoboron Compounds in Organic Synthesis*, Harwood Academics, Glasgow.

7 Vaultier, M. and Carboni, B. (1995) Chapter 9, in *Comprehensive Organometallic Chemistry II*, vol. **11** (eds E.V. Abel and G. Wilkinson), Pergamon Press, Oxford, pp. 191–276.

8 Kaufmann, D.E. and Matteson, D.S. (eds) (2003) *Science of Synthesis: Vol. 6: Boron Compounds*, Thieme, Stuttgart, Germany.

9 Rettig, S.J. and Trotter, T. (1977) *Can. J. Chem.*, **55**, 3071–3075.

10 Cambridge Crystallographic Database Compound (CCDC) number 222652 (www.ccdc.cam.ac.uk).

11 Soundararajan, S., Duesler, E.N., and Hageman, J.H. (1993) *Acta Crystallogr.*, **C49**, 690–693.

12 Parry, P.R., Wang, C., Batsanov, A.S., Bryce, M.R., and Tarbit, B. (2002) *J. Org. Chem.*, **67**, 7541–7543 (CCDC numbers: bromide, 184781 and 184782; chloride, 184783).

13 Fournier, J.-H., Maris, T., Wuest, J.D., Guo, W., and Galoppini, E. (2003) *J. Am. Chem. Soc.*, **125**, 1002–1006.

14 Sana, M., Leroy, G., and Wilante, C. (1991) *Organometallics*, **10**, 264–270.

15 Ho, O.C., Soundararajan, R., Lu, J., Matteson, D.S., Wang, Z., Chen, X., Wei, M., and Willett, R.D. (1995) *Organometallics*, **14**, 2855–2860.

16 Zhdankin, V.V., Persichini, P.J., III, Zhang, L., Fix, S., and Kiprof, P. (1999) *Tetrahedron Lett.*, **40**, 6705–6708.

17 Adamczyk-Wozniak, A., Cyranski, M.K., Zubrowska, A., and Sporzynski, A. (2009) *J. Organomet. Chem.*, **694**, 3533–3541.

18 Rettig, S.J. and Trotter, J. (1975) *Can. J. Chem.*, **53**, 1393–1401.

19 Csuk, R., Müler, N., and Sterk, H. (1985) *Z. Naturforsch. B*, **40**, 987–989.

20 Mancilla, T., Contreras, R., and Wrackmeyer, B. (1986) *J. Organomet. Chem.*, **307**, 1–6.

21 Bien, J.T., Eschner, M.J., and Smith, B.D. (1995) *J. Org. Chem.*, **60**, 4525–4529.

22 Matteson, D.S., Michnick, T.J., Willett, R.D., and Patterson, C.D. (1989) *Organometallics*, **8**, 726–729.

23 Cammidge, A.N., Goddard, V.H.M., Gopee, H., Harrison, N.L., Hughes, D.L., Schubert, C.J., Sutton, B.M., Watts, G.C., and Whitehead, A.J. (2006) *Org. Lett.*, **8**, 4071–4074.

24 Kaiser, P.F., White, J.M., and Hutton, C.A. (2008) *J. Am. Chem. Soc.*, **130**, 16450–16451.

25 Matteson, D.S. (1995) Chapter 1, in *Stereodirected Synthesis with Organoboranes*, Springer, Berlin, pp. 1–20.

26 (a) Yamashita, M., Yamamoto, Y., Akiba, K.-y., and Nagase, S. (2000) *Angew. Chem., Int. Ed.*, **39**, 4055–4058; (b) Yamashita, M., Yamamoto, Y., Akiba, K.-y., Hashizume, D., Iwasaki, F., Takagi, N., and Nagase, S. (2005) *J. Am. Chem. Soc.*, **127**, 4354–4371.

27 Yamashita, M., Kamura, K., Yamamoto, Y., and Akiba, K.-y. (2002) *Chem. Eur. J.*, **8**, 2976–2979.

28 Yamamoto, Y. and Moritani, I. (1975) *J. Org. Chem.*, **40**, 3434–3437.

29 Matteson, D.S. (1970) *Progress in Boron Chemistry*, vol. **3** (eds R.J. Brotherton and H. Steinberg), Pergamon, New York, pp. 117–176.

30 Good, C.D. and Ritter, D.M. (1962) *J. Am. Chem. Soc.*, **84**, 1162–1166.

31 Hall, L.W., Odom, J.D., and Ellis, P.D. (1975) *J. Am. Chem. Soc.*, **97**, 4527–4531.

32 Holliday, A.K., Reade, W., Johnstone, R.A.W., and Neville, A.F. (1971) *J. Chem. Soc., Chem. Commun.*, 51–52.

33 Bachler, V. and Metzler-Nolte, N. (1998) *Eur. J. Inorg. Chem.*, 733–744.

34 Beachell, H.C. and Beistel, D.W. (1964) *Inorg. Chem.*, **3**, 1028–1032.

35 Matteson, D.S. and Mah, R.W.H. (1963) *J. Org. Chem.*, **28**, 2171–2174.

36 Matteson, D.S. (1962) *J. Org. Chem.*, **27**, 4293–4300.

37 (a) Matteson, D.S. and Peacock, K. (1960) *J. Am. Chem. Soc.*, **82**, 5759–5760; (b) Matteson, D.S. and Waldbillig, J.O. (1963) *J. Org. Chem.*, **28**, 366–369.

38 Matteson, D.S. and Talbot, M.L. (1967) *J. Am. Chem. Soc.*, **89**, 1123–1126.

39 Evans, D.A., Golob, A.M., Mandel, N.S., and Mandel, G.S. (1978) *J. Am. Chem. Soc.*, **100**, 8170–8174.

40 Singleton, D.A. (1992) *J. Am. Chem. Soc.*, **114**, 6563–6564.

41 Knapp, D.M., Gillis, E.P., and Burke, M.D. (2009) *J. Am. Chem. Soc.*, **131**, 6961–6963.

42 Snyder, H.R., Kuck, J.A., and Johnson, J.R. (1938) *J. Am. Chem. Soc.*, **60**, 105–111.

43 Johnson, J.R. and Van Campen, M.G., Jr. (1938) *J. Am. Chem. Soc.*, **60**, 121–124.

44 Soloway, A.H., Whitman, B., and Messer, J.R. (1960) *J. Pharmacol. Exp. Ther.*, **129**, 310–314.

45 Benderdour, M., Bui-Van, T., Dicko, A. *et al.* (1998) *J. Trace Elem. Med. Biol.*, **12**, 2–7.

46 Soloway, A.H., Whitman, B., and Messer, J.R. (1962) *J. Med. Pharm. Chem.*, **7**, 640.

47 Soloway, A.H. (1958) *Science*, **128**, 1572.

48 Matteson, D.S., Soloway, A.H., Tomlinson, D.W., Campbell, J.D., and Nixon, G.A. (1964) *J. Med. Chem.*, **7**, 640–643.

49 Weir, R.J., Jr., and Fisher, R.S. (1972) *Toxicol. Appl. Pharmacol.*, **23**, 351.

50 Linden, C.H., Hall, A.H., and Kulig, K.W. (1986) *J. Toxicol. Clin. Toxicol.*, **24**, 269–279.

51 Restuccio, A., Mortensen, M.E., and Kelley, M.T. (1992) *Am. J. Emerg. Med.*, **10**, 545–547.

52 Lorand, J.P. and Edwards, J.O. (1959) *J. Org. Chem.*, **24**, 769–774.

53 Branch, G.E.K., Yabroff, D.L., and Bettmann, B. (1934) *J. Am. Chem. Soc.*, **56**, 937–941.

54 Yabroff, D.L., Branch, G.E.K., and Bettmann, B. (1934) *J. Am. Chem. Soc.*, **56**, 1850–1857.

55 Bettman, B., Branch, G.E.K., and Yabroff, D.L. (1934) *J. Am. Chem. Soc.*, **56**, 1865–1870.

56 Soundararajan, S., Badawi, M., Kohlrust, C.M., and Hageman, J.H. (1989) *Anal. Biochem.*, **178**, 125–134.

57 Yan, J., Springsteen, G., Deeter, S., and Wang, B.H. (2004) *Tetrahedron*, **60**, 11205–11209.

58 Babcock, L. and Pizer, R. (1980) *Inorg. Chem.*, **19**, 56–61.

59 Westmark, P.R., Gardiner, S.J., and Smith, B.D. (1996) *J. Am. Chem. Soc.*, **118**, 11093–11100.

60 Torssell, K., McLendon, J.H., and Somers, G.F. (1958) *Acta Chem. Scand.*, **12**, 1373–1385.

61 Settepani, J.A., Stokes, J.B., and Borkovek, A.B. (1970) *J. Med. Chem.*, **13**, 128–131.

62 Torssell, T. (1964) *Progress in Boron Chemistry*, vol. **1** (eds H. Steinberg and A.L. McCloskey), Pergamon, New York, pp. 369–415.

63 Mulla, H.R., Agard, N.J., and Basu, A. (2004) *Bioorg. Med. Chem. Lett.*, **14**, 25–27.

64 Fisher, F.C. and Havinga, E. (1974) *Recl. Trav. Chim. Pays Bas*, **93**, 21–24.

65 Yang, W., Yan, J., Springsteen, G., Deeter, S., and Wang, B. (2003) *Bioorg. Med. Chem. Lett.*, **13**, 1019–1022.

66 (a) Wulff, G. (1982) *Pure Appl. Chem.*, **54**, 2093–2102; (b) Wiskur, S.L., Lavigne, J.J., Ait-Haddou, H., Lynch, V., Chiu, Y.H., Canary, J.W., and Anslyn, E.W. (2001) *Org. Lett.*, **3**, 1311–1314; (c) Juillard, J. and Geuguen, N. (1967) *C.R. Acad. Sci (Paris)*, **C264**, 259–261.

67 McDaniel, D.H. and Brown, H.C. (1955) *J. Am. Chem. Soc.*, **77**, 3756–3763.

68 Singhal, R.P., Ramamurthy, B., Govindraj, N., and Sarwar, Y. (1991) *J. Chromatogr.*, **543**, 17–38.

69 (a) Ni, W.J., Kaur, G., Springsteen, G., Franzen, S., and Wang, B. (2004) *Bioorg. Chem.*, **32**, 571–581; (b) Zhu, L., Shabbir, S.H., Gray, M., Lynch, V.M., Sorey, S., and Anslyn, E.V. (2006) *J. Am. Chem. Soc.*, **128**, 1222–1232; (c) Collins, B.E., Sorey, S., Hargrove, A.E., Shabbir, S.H., Lynch, V.M., and Anslyn, E.V. (2009) *J. Org. Chem.*, **74**, 4055–4060.

70 Ainley, A.D. and Challenger, F. (1930) *J. Chem. Soc.*, 2171–2180.

71 Dewar, M.J.S. and Jones, R. (1967) *J. Am. Chem. Soc.*, **89**, 2408–2410.

72 Dewar, M.J.S. (1964) *Progress in Boron Chemistry*, vol. 1 (eds H. Steinberg and A.L. McCloskey), Pergamon, New York, pp. 235–263.

73 Carboni, B. and Monnier, L. (1999) *Tetrahedron*, **55**, 1197–1248.

74 Yabroff, D.L. and Branch, G.E.K. (1933) *J. Am. Chem. Soc.*, **55**, 1663–1665.

75 Snyder, H.R., Konecky, M.S., and Lennarz, W.J. (1958) *J. Am. Chem. Soc.*, **80**, 3611–3615.

76 Reetz, M.T., Niemeyer, C.M., and Harms, K. (1991) *Angew. Chem., Int. Ed. Engl.*, **30**, 1472–1474.

77 Reetz, M.T., Niemeyer, C.M., Hermes, M., and Goddard, R. (1992) *Angew. Chem., Int. Ed. Engl.*, **31**, 1017–1019.

78 Reetz, M.T., Huff, J., and Goddard, R. (1994) *Tetrahedron Lett.*, **35**, 2521–2524.

79 Nozaki, K., Yoshida, M., and Takaya, H. (1994) *Angew. Chem., Int. Ed. Engl.*, **33**, 2452–2454.

80 Nozaki, K., Tsutsumi, T., and Takaya, H. (1995) *J. Org. Chem.*, **60**, 6668–6669.

81 Sakurai, H., Iwasawa, N., and Narasaka, K. (1996) *Bull. Chem. Soc. Jpn.*, **69**, 2585–2594.

82 Katz, H.E. (1989) *J. Org. Chem.*, **54**, 2179–2183.

83 Lemieux, V., Spantulescu, M.D., Baldridge, K.K., and Branda, N.R. (2008) *Angew. Chem. Int. Ed.*, **47**, 5034–5037.

84 Hawkins, V.F., Wilkinson, M.C., and Whiting M. (2008) *Org. Proc. Res. Devel.*, **12**, 1265–1268.

85 Johnson, J.R., Van Campen, M.G., Jr., and Grummit, O. (1938) *J. Am. Chem. Soc.*, **60**, 111–115.

86 Challenger, F. and Richards, O.V. (1934) *J. Chem. Soc.*, 405–411.

87 Snyder, H.R. and Wyman, F.W. (1948) *J. Am. Chem. Soc.*, **70**, 234–237.

88 Kuivila, H.G. and Nahabedian, K.V. (1961) *J. Am. Chem. Soc.*, **83**, 2159–2163.

89 Soloway, A.H. (1959) *J. Am. Chem. Soc.*, **81**, 3017–3019.

90 Dick, G.R., Knapp, D.M., Gillis, E.P., and Burke, M.D. (2010) *Org. Lett.*, **12**, 2314–2317.

91 (a) Kuivila, H.G. and Nahabedian, K.V. (1961) *J. Am. Chem. Soc.*, **83**, 2164–2166; (b) Nahabedian, K.V. and Kuivila, H.G. (1961) *J. Am. Chem. Soc.*, **83**, 2167–2174.

92 McKiernan, G.J. and Hartley, R.C. (2003) *Org. Lett.*, **5**, 4389–4392.

93 Mothana, S., Chahal, N., Vanneste, S., and Hall, D.G. (2007) *J. Comb. Chem.*, **9**, 193–196.

94 Beckett, M.A., Gilmore, R.J., and Idrees, K. (1993) *J. Organomet. Chem.*, **455**, 47–49.

95 (a) Brown, H.C., Basavaiah, D., and Kulkarni, S.U. (1982) *J. Org. Chem.*, **47**, 3808–3810; (b) Brown, H.C., Basavaiah, D., Kulkarni, S.U., Lee, H.D., Negishi, E.-i., and Katz, J.J. (1986) *J. Org. Chem.*, **51**, 5270–5276.

96 Korich, A.L. and Iovine, P.M. (2010) *Dalton Trans.*, **39**, 1423–1431.

97 Schleyer, P.V., Jiao, H.J., Hommes, N.J.R.V., Malkin, V.G., and Malkina, O.L. (1997) *J. Am. Chem. Soc.*, **119**, 12669–12770.

98 Brock, C.P., Minton, R.P., and Niedenzu, K. (1987) *Acta Crystallogr.*, **C43**, 1775–1779.

99 Morgan, A.B., Jurs, J.L., and Tour, J.M. (2000) *J. Appl. Polym. Sci.*, **76**, 1257–1268.

100 Côté, A.P., Benin, A.I., Ockwig, N.W., O'Keefe, M., Matzger, A.J., and Yaghi, O.M. (2005) *Science*, **310**, 1166–1170.

101 Li, Y., Ding, J., Day, M., Tao, Y., Lu, J., and D'iorio, M. (2003) *Chem. Mater.*, **15**, 4936–4943.

102 Tokunaga, Y., Ueno, H., Shimomura, Y., and Seo, T. (2002) *Heterocycles*, **57**, 787–790.

103 Farfan, N., Höpfl, H., Barba, V., Ochoa, ME., Santillan, R., Gómez, E., and Gutiérrez, A. (1999) *J. Organomet. Chem.*, **581**, 70–81, and references cited therein.

104 Schnürch, M., Holzweber, M., Mihovilovic, M.D., and Stanetty, P. (2007) *Green Chem.*, **9**, 139–145.

105 Garlaschelli, L., Mellerio, G., and Vidari, G. (1989) *Tetrahedron Lett.*, **30**, 597–600.

106 Dahlhoff, W.V. and Köster, R. (1982) *Heterocycles*, **18**, 421–449.

107 Kuivila, H.G., Keough, A.H., and Soboczenski, E.J. (1954) *J. Org. Chem.*, **8**, 780–783.

108 Sugihara, J.M. and Bowman, C.M. (1958) *J. Am. Chem. Soc.*, **80**, 2443–2446.

109 Meiland, M., Heinze, T., Guenther, W., and Liebert, T. (2009) *Tetrahedron Lett.*, **50**, 469–472.

110 Ahn, Y.H. and Chang, Y.-T. (2004) *J. Comb. Chem.*, **6**, 293–296.

111 (a) Roy, C.D. and Brown, H.C. (2007) *J. Organomet. Chem.*, **692**, 784–790; (b) Roy, C.D. and Brown, H.C. (2007) *Monatsh. Chem.*, **138**, 879–887.

112 (a) Letsinger, R.L. and Skoog, I. (1955) *J. Am. Chem. Soc.*, **77**, 2491–2494; (b) Musgrave, O.C. and Park, T.O. (1955) *Chem. Ind. (London)*, **48**, 1552.

113 Weidman, H. and Zimmerman, H.K., Jr. (1958) *Justus Liebigs Ann. Chem.*, **619**, 28–35.

114 (a) Haruta, R., Ishiguro, M., Ikeda, N., and Yamamoto, Y. (1982) *J. Am. Chem. Soc.*, **104**, 7667–7669; (b) Roush, W.R., Walts, A.G., and Hoong, L.K. (1985) *J. Am. Chem. Soc.*, **107**, 8186–8190.

115 Ketuly, K.A. and Hadi, A.H.A. (2010) *Molecules*, **15**, 2347–2356.

116 Ditrich, K., Bube, T., Stürmer, R., and Hoffmann, R.W. (1986) *Angew. Chem., Int. Ed. Engl.*, **25**, 1028–1030.

117 Matteson, D.S. and Kandil, A.A. (1986) *Tetrahedron Lett.*, **27**, 3831–3834.

118 Ray, R. and Matteson, D.S. (1980) *Tetrahedron Lett.*, **21**, 449–450.

119 Herold, T., Schrott, U., and Hoffmann, R.W. (1981) *Chem. Ber.*, **111**, 359–374.

120 (a) Luithle, J.E.A. and Pietruszka, J. (1999) *J. Org. Chem.*, **64**, 8287–8297; (b) Luithle, J.E.A. and Pietruszka, J. (2000) *J. Org. Chem.*, **65**, 9194–9200; (c) Pietruszka, J. and Solduga, G. (2009) *Eur. J. Org. Chem.*, 5998–6008.

121 Matteson, D.S. and Ray, R. (1980) *J. Am. Chem. Soc.*, **102**, 7590–7591.

122 Matteson, D.S., Sadhu, K.M., and Lienhard, G.E. (1981) *J. Am. Chem. Soc.*, **103**, 5241–5242.

123 Matteson, D.S., Ray, R., Rocks, R.R., and Tsai, D.J.S. (1983) *Organometallics*, **2**, 1536–1543.

124 Matteson, D.S. and Sadhu, K.M. (1984) *Organometallics*, **3**, 614–618.

125 Martichonok, V. and Jones, J.B. (1996) *J. Am. Chem. Soc.*, **118**, 950–958.

126 Brown, H.C. and Rangaishenvi, M.V. (1988) *J. Organomet. Chem.*, **358**, 15–30.

127 Matteson, D.S. and Kim, G.Y. (2002) *Org. Lett.*, **4**, 2153–2155.

128 Inglis, S.R., Woon, E.C.Y., Thompson, A.L., and Schofield, C.J. (2010) *J. Org. Chem.*, **75**, 468–471.

129 Yuen, A.K.L. and Hutton, C.A. (2005) *Tetrahedron Lett.*, **46**, 7899–7903.

130 Pennington, T.E., Cynantya, K.B., and Hutton, C.A. (2004) *Tetrahedron Lett.*, **45**, 6657–6660.

131 Wityak, J., Earl, R.A., Abelman, M.M., Bethel, Y.B., Fisher, B.N., Kauffman, G.S., Kettner, C.A., Ma, P., McMillan, J.L., Mersinger, L.J., Pesti, J., Pierce, M.E., Rankin, F.W., Chorvat, R.J., and Confalone, P.N. (1995) *J. Org. Chem.*, **60**, 3717–3722.

132 Coutts, S.J., Adams, J., Krolikowski, D., and Snow, R.J. (1994) *Tetrahedron Lett.*, **35**, 5109–5112.

133 Yan, J., Jin, S., and Wang, B. (2005) *Tetrahedron Lett.*, **46**, 8503–8505.

134 Bowie, R.A. and Musgrave, O.C. (1963) *J. Chem. Soc., Chem. Commun.*, 3945–3949.

135 Matteson, D.S. and Man, H.W. (1996) *J. Org. Chem.*, **61**, 6047–6051.

136 Matteson, D.S., Soundararajan, R., Ho, O.C., and Gatzweiler, W. (1996) *Organometallics*, **15**, 152–163.

137 Tripathy, P.B. and Matteson, D.S. (1990) *Synthesis*, 200–206.

138 Kettner, C.A. and Shenvi, A.B. (1984) *J. Biol. Chem.*, **259**, 15106–15114.

139 Wulff, G., Lauer, M., and Böhnke, H. (1984) *Angew. Chem., Int. Ed. Engl.*, **23**, 741–742.

140 Edwards, J.O., Morrison, G.C., Ross, V., and Schultz, J.W. (1955) *J. Am. Chem. Soc.*, **77**, 266–268.

141 Springsteen, G. and Wang, B. (2002) *Tetrahedron*, **58**, 5291–5300.

142 Barker, S.A., Chopra, A.K., Hatt, B.W., and Somers, P.J. (1973) *Carbohydr. Res.*, **26**, 33–40.

143 Pizer, R. and Tihal, C. (1992) *Inorg. Chem.*, **31**, 3243–3247.

144 Iwatsuki, S., Nakajima, S., Inamo, M., Takagi, H.D., and Ishihara, K. (2007) *Inorg. Chem.*, **46**, 354–356.

145 Iwasawa, N. and Takahagi, H. (2007) *J. Am. Chem. Soc.*, **129**, 7754–7755.

146 Bielecki, M., Eggert, H., and Norrild, J.C. (1999) *J. Chem. Soc., Perkin Trans. 2*, 449–455.

147 Draffin, S.P., Duggan, P.J., and Fallon, G.D. (2004) *Acta Crystallogr. E*, **E60**, o1520–o1522.

148 Draffin, S.P., Duggan, P.J., Fallon, G.D., and Tyndall, E.M. (2005) *Acta Crystallogr. E*, **E61**, o1733–o1735.

149 Nagai, Y., Kobayashi, K., Toi, H., and Aoyama, Y. (1993) *Bull. Chem. Soc. Jpn.*, **66**, 2965–2971.

150 Stones, D., Manku, S., Lu, L., and Hall, D.G. (2004) *Chem. Eur. J.*, **10**, 92–100.

151 (a) Dowlut, M. and Hall, D.G. (2006) *J. Am. Chem. Soc.*, **128**, 4226–4227; (b) Bérubé, M., Dowlut, M., and Hall, D.G. (2008) *J. Org. Chem.*, **73**, 6471–6479.

152 (a) Springsteen, G. and Wang, B. (2001) *Chem. Commun.*, 1608–1609; (b) Arimori, S. and James, T.D. (2002) *Tetrahedron Lett.*, **43**, 507–509.

153 Bosch, L.I., Fyles, T.M., and James, T.D. (2004) *Tetrahedron*, **60**, 11175–11190.

154 Bromba, C., Carrie, P., Chui, J.K.W., and Fyles, T.M. (2009) *Supramol. Chem.*, **21**, 81–88.

155 Gillis, E.P. and Burke, M.D. (2007) *J. Am. Chem. Soc.*, **129**, 6716–6717.

156 Gillis, E.P. and Burke, M.D. (2009) *Aldrichimica Acta*, **42**, 17–27.

157 Woods, W.G. and Strong, P.L. (1966) *J. Am. Chem. Soc.*, **88**, 4667–4671.

158 Brown, H.C. and Gupta, S.K. (1971) *J. Am. Chem. Soc.*, **93**, 1816–1818.

159 Tucker, C.E., Davidson, J., and Knochel, P. (1992) *J. Org. Chem.*, **57**, 3482–3485.

160 Panek, J.S. and Xu, F. (1992) *J. Org. Chem.*, **57**, 5288–5290.

161 Thaisrivongs, S. and Wuest, J.D. (1977) *J. Org. Chem.*, **42**, 3243–3246.

162 (a) Furuta, K., Miwa, Y., Iwanaga, K., and Yamamoto, H. (1988) *J. Am. Chem. Soc.*, **110**, 6254–6255; (b) Furuta, K., Maruyama, T., and Yamamoto, H. (1991) *J. Am. Chem. Soc.*, **113**, 1041–1042.

163 (a) Takasu, M. and Yamamoto, H. (1990) *Synlett.*, 194–196; (b) Sartor, D., Saffrich, J., and Helmchen, G. (1990) *Synlett.*, 197–198; (c) Kiyooka, S.-i., Kaneko, Y., Komura, M., Matsuo, H., and Nakano, M. (1991) *J. Org. Chem.*, **56**, 2276–2278.

164 (a) Marder, T.B. and Norman, N.C. (1998) *Top. Catal.*, **5**, 63–73; (b) Ishiyama, T. and Miyaura, N. (2000) *J. Organomet. Chem.*, **611**, 392–402.

165 Iwadate, N. and Suginome, M. (2010) *J. Am. Chem. Soc.*, **132**, 2548–2549.

166 Ishiyama, T., Murata, M., Ahiko, T.-a., and Miyaura, N. (2000) *Org. Synth.*, **77**, 176–182.

167 Anastasi, N.R., Waltz, K.M., Weerakoon, W.L., and Hartwig, J.F. (2003) *Organometallics*, **22**, 365–369.

168 Letsinger, R.L. and Hamilton, S.B. (1958) *J. Am. Chem. Soc.*, **80**, 5411–5413.

169 Dewar, M.J.S., Kubba, V.P., and Pettit, R. (1958) *J. Chem. Soc.*, 3076–3079.

170 Hawkins, R.T. and Snyder, H.R. (1960) *J. Am. Chem. Soc.*, **82**, 3863–3866.

171 Noguchi, H., Hojo, K., and Suginome, M. (2007) *J. Am. Chem. Soc.*, **129**, 758–759.

172 Yanagisawa, A., Inanami, H., and Yamamoto, H. (1998) *Chem. Commun.*, 1573–1574.

173 Mohler, L.K. and Czarnik, A.W. (1993) *J. Am. Chem. Soc.*, **115**, 7037–7038.

174 Shull, B.K., Spielvogel, D.E., Gopalaswamy, R., Sankar, S., Boyle, P.D.,

Head, G., and Devito, K. (2000) *J. Chem. Soc., Perkin Trans. 2*, 557–561.

175 (a) Chissick, S.S., Dewar, M.J.S., and Maitlis, P.M. (1959) *J. Am. Chem. Soc.*, **81**, 6329–6330; (b) Chissick, S.S., Dewar, M.J.S., and Maitlis, P.M. (1961) *J. Am. Chem. Soc.*, **83**, 2708–2711.

176 Pailer, M. and Fenzl, W. (1961) *Monatsh. Chem.*, **92**, 1294–1299.

177 Stolowitz, M.L., Ahlem, C., Hughes, K.A., Kaiser, R.J., Kesicki, E.A., Li, G., Lund, K.P., Torkelson, S.M., and Wiley, J.P. (2001) *Bioconjug. Chem.*, **12**, 229–239.

178 (a) Corey, E.J. and Loh, T.-P. (1991) *J. Am. Chem. Soc.*, **113**, 8966–8967; (b) Corey, E.J., Cywin, C.L., and Roper, T.D. (1992) *Tetrahedron Lett.*, **33**, 6907–6010; (c) Ishihara, K., Kondo, S., and Yamamoto, H. (2000) *J. Org. Chem.*, **65**, 9125–9128; (d) Kinugasa, M., Harada, T., and Oku, A. (1997) *J. Am. Chem. Soc.*, **119**, 9067–9068.

179 Vedejs, E., Chapman, R.W., Lin, S., Müller, M., and Powell, D.R. (2000) *J. Am. Chem. Soc.*, **122**, 3047–3052.

180 Corey, E.J. (2002) *Angew. Chem., Int. Ed.*, **41**, 1650–1667.

181 (a) Corey, E.J. and Helal, C.J. (1998) *Angew. Chem., Int. Ed.*, **37**, 1986–2012; (b)Cho, B.T. (2006) *Tetrahedron*, **62**, 7621–7643.

182 Corey, E.J. (2009) *Angew. Chem., Int. Ed.*, **48**, 2100–2117.

183 Groziak, M.P., Ganguly, A.D., and Robinson, P.D. (1994) *J. Am. Chem. Soc.*, **116**, 7597–7605.

184 Snyder, H.R., Reedy, A.J., and Lennarz, W.J. (1958) *J. Am. Chem. Soc.*, **80**, 835–838.

185 Lennarz, W.J. and Snyder, H.R. (1960) *J. Am. Chem. Soc.*, **82**, 2172–2175.

186 (a) Soloway, A.H. (1960) *J. Am. Chem. Soc.*, **82**, 2442–2444; (b) Dewar, M.J.S. and Dougherty, R.C. (1964) *J. Am. Chem. Soc.*, **86**, 433–436; (c) Tschampel, P. and Snyder, H.R. (1964) *J. Org. Chem.*, **29**, 2168–2172; (d) Matteson, D.S., Biernbaum, M.S., Bechtold, R.A., Campbell, J.D., and Wilcsek, R.J. (1978) *J. Org. Chem.*, **43**, 950–954; (e) Boldyreva, O., Dorokhov, V.A., and Mikhailov, B.M. (1985) *Izv. Akad. Nauk SSSR, Ser. Khim.*, 428–430; (f) Hughes, M.P. and Smith, B.D. (1997) *J. Org. Chem.*, **62**, 4492–4499; (g) Zhuo, J.-C., Soloway, A.H., Beeson, J.C., Ji, W., Barnum, B.A., Rong, F.-G., Tjarks, W., Jordan, G.T., IV, Liu, J., and Shore, S.G. (1999) *J. Org. Chem.*, **64**, 9566–9574; (h) Ruman, T., Dlugopolska, K., Kusnierz, A., Jurkiewicz, A., Les, A., and Rode, W. (2009) *Bioorg. Chem.*, **37**, 65–69; (i) Ruman, T., Dlugopolska, K., Kusnierz, A., and Rode, W. (2009) *Bioorg. Chem.*, **37**, 180–184; (j) Ruman, T., Dlugopolska, K., and Rode, W. (2010) *Bioorg. Chem.*, **38**, 33–36.

187 Robinson, P.D., Groziak, M.P., and Yi, L. (1996) *Acta Crystallogr.*, **C52**, 2826–2830.

188 Matteson, D.S. and Cheng, T.-C. (1968) *J. Org. Chem.*, **33**, 3055–3060.

189 Brown, H.C., Salunkhe, A.M., and Argade, A.B. (1992) *Organometallics*, **11**, 3094–3097.

190 Brown, H.C., Cole, T.E., Bakshi, R.K., Srebnik, M., and Singaram, B. (1986) *Organometallics*, **5**, 2303–2307.

191 Brown, H.C., Salunkhe, A.M., and Singaram, B. (1991) *J. Org. Chem.*, **56**, 1170–1175.

192 Brown, H.C., Cole, T.E., and Singaram, B. (1984) *Organometallics*, **3**, 774–777.

193 (a) Vedejs, E., Chapman, R.W., Fields, S.C., Lin, S., and Schrimpf, M.R. (1995) *J. Org. Chem.*, **60**, 3020–3027; (b) Vedejs, E., Fields, S.C., Hayashi, R., Hitchcock, S.R., Powell, D.R., and Schrimpf, M.R. (1999) *J. Am. Chem. Soc.*, **121**, 2460–2470.

194 (a) Darses, S. and Genêt, J.-P. (2003) *Eur. J. Org. Chem.*, 4313–4327; (b) Molander, G.A. and Ellis, N. (2007) *Acc. Chem. Res.*, **40**, 275–286.

195 Ting, R., Harwig, C., auf der Keller, U., McCormick, S., Austin, P., Overall, C.M., Adam, M.J., Ruth, T.J., and Perrin, D.M. (2008) *J. Am. Chem. Soc.*, **130**, 12045–12055.

196 Kim, B.J. and Matteson, D.S. (2004) *Angew. Chem., Int. Ed.*, **43**, 3056–3058.

197 Molander, G.A. and Ribagorda, M. (2003) *J. Am. Chem. Soc.*, **125**, 11148–11149.

198 Yamamoto, Y., Takizawa, M., Yu, X.-Q., and Miyaura, N. (2008) *Angew. Chem., Int. Ed.*, **47**, 928–931.

199 Gilman, H. and Moore, L.O. (1958) *J. Am. Chem. Soc.*, **80**, 3609–3611.

200 (a) Khotinsky, E. and Melamed, M. (1909) *Ber. Dtsch. Chem. Ges.*, **54**, 2784; (b) Khotinsky, E. and Melamed, M. (1909) *Ber. Dtsch. Chem. Ges.*, **42**, 3090.

201 Krause, E. and Nitsche, R. (1921) *Ber. Dtsch. Chem. Ges.*, **55**, 1261–1265.

202 Seaman, W. and Johnson, J.R. (1931) *J. Am. Chem. Soc.*, **53**, 711–723.

203 Bean, F.R. and Johnson, J.R. (1932) *J. Am. Chem. Soc.*, **54**, 4415–4425.

204 Cladingboel, D.E. (2000) *Org. Process Res. Dev.*, **4**, 153–155.

205 Zenk, R. and Partzsch, S. (2003) *Chim. Oggi*, **21**, 70–73.

206 Jendralla, H., Wagner, A., Mollath, M., and Wunner, J. (1995) *Liebigs Ann.*, 1253–1257.

207 Brown, H.C. and Cole, T.E. (1983) *Organometallics*, **2**, 1316–1319.

208 Brown, H.C., Srebnik, M., and Cole, T.E. (1986) *Organometallics*, **5**, 2300–2303.

209 Li, W., Nelson, D.P., Jensen, M.S., Hoerrner, R.S., Cai, D., Larsen, R.D., and Reider, P.J. (2002) *J. Org. Chem.*, **67**, 5394–5397.

210 Das, S., Alexeev, V.L., Sharma, A.C., Geib, S.J., and Asher, S.A. (2003) *Tetrahedron Lett.*, **44**, 7719–7722.

211 Evans, D.A., Katz, J.L., Peterson, G.S., and Hintermann, T. (2001) *J. Am. Chem. Soc.*, **123**, 12411–12413.

212 Gilman, H., Santucci, L., Swayampati, D.R., and Ranck, R.D. (1957) *J. Am. Chem. Soc.*, **79**, 3077–3081.

213 Knochel, P., Dohle, W., Gommermann, N., Kneisel, F.F., Kopp, F., Korn, T., Sapountzis, I., and Vu, V.A. (2003) *Angew. Chem., Int. Ed.*, **42**, 4302–4320.

214 (a) Collibee, S.E. and Yu, J. (2005) *Tetrahedron Lett.*, **46**, 4453–4455; (b) Demory, E., Blandin, V., Einhorn, J., and Chavant, P. Y. (2011) *Org. Process Res. Dev.* **15**, 710–716.

215 Wong, K.-T., Chien, Y.Y., Liao, Y.-L., Lin, C.-C., Chou, M.Y., and Leung, M.-K. (2002) *J. Org. Chem.*, **67**, 1041–1044.

216 Garg, N.K., Sarpong, R., and Stoltz, B.M. (2002) *J. Am. Chem. Soc.*, **124**, 13179–13184.

217 Chavant, P.Y. and Vaultier, M. (1993) *J. Organomet. Chem.*, **455**, 37–46.

218 Marr, G., Moore, R.E., and Rockett, B.W. (1967) *J. Organomet. Chem.*, **7**, P11–P13.

219 Hawkins, R.T. and Stroup, D.B. (1969) *J. Org. Chem.*, **34**, 1173–1174.

220 Lauer, M. and Wulff, G. (1983) *J. Organomet. Chem.*, **256**, 1–9.

221 Sharp, M.J. and Snieckus, V. (1985) *Tetrahedron Lett.*, **49**, 5997–6000.

222 Sharp, M.J., Cheng, W., and Snieckus, V. (1987) *Tetrahedron Lett.*, **28**, 5093–5096.

223 Alo, B.I., Kandil, A., Patil, P.A., Sharp, M.J., Siddiqui, M.A., and Snieckus, V. (1991) *J. Org. Chem.*, **96**, 3763–3768.

224 Larsen, R.D., King, A.O., Chen, C.Y., Corley, E.G., Foster, B.S., Roberts, F.E., Yang, C., Lieberman, D.R., Reamer, R.A., Tschaen, D.M., Verhoeven, T.R., Reider, P.J., Lo, Y.S., Rossano, L.T., Brookes, A.S., Meloni, D., Moore, J.R., and Arnett, J.F. (1994) *J. Org. Chem.*, **59**, 6391–6394.

225 Antoft-Finch, A., Blackburn, T., and Snieckus, V. (2009) *J. Am. Chem. Soc.*, **131**, 17750–17752.

226 Caron, S. and Hawkins, J.M. (1998) *J. Org. Chem.*, **63**, 2054–2055.

227 Kristensen, J., Lysén, M., Vedso, P., and Begtrup, M. (2001) *Org. Lett.*, **3**, 1435–1437.

228 (a) Michaelis, A. and Becker, P. (1880) *Ber. Dtsch. Chem. Ges.*, **13**, 58; (b) Michaelis, A. and Becker, P. (1882) *Ber. Dtsch. Chem. Ges.*, **15**, 180–185.

229 Breuer, S.W., Thorpe, F.G., and Podestá, J.C. (1974) *Tetrahedron Lett.*, **42**, 3719–3720.

230 Haubold, W., Herdtle, J., Gollinger, W., and Einholz, W. (1986) *J. Organomet. Chem.*, **315**, 1–8.

231 Zhao, Z. and Snieckus, V. (2005) *Org. Lett.*, **7**, 2523–2526.

232 Ishiyama, T., Murata, M., and Miyaura, N. (1995) *J. Org. Chem.*, **60**, 7508–7510.

233 (a) Murata, M., Watanabe, S., and Masuda, Y. (1997) *J. Org. Chem.*, **62**, 6458–6459; (b) Murata, M., Oyama, T., Watanabe, S., and Masuda, Y. (2000) *J. Org. Chem.*, **65**, 164–168; (c) Baudoin, O., Guénard, D., and Guéritte, F. (2000) *J. Org. Chem.*, **65**, 9268–9271.

234 Baudoin, O., Décor, A., Cesario, M., and Guéritte, F. (2003) *Synlett*, 2009–2012.

235 Song, Y.-L. and Morin, C. (2001) *Synlett*, 266–268.

236 Yoburn, J.-C. and Van Vranken, D.L. (2003) *Org. Lett.*, **5**, 2817–2820.

237 Lin, S. and Danishefsky, S.J. (2001) *Angew. Chem., Int. Ed.*, **40**, 1967–1970.

238 (a) Fang, H., Kaur, G., Yan, J., and Wang, B. (2005) *Tetrahedron Lett.*, **46**, 1671–1674; (b) Diemer, V., Chaumeil, H., Defoin, A., and Carré, C. (2010) *Tetrahedron*, **66**, 918–929.

239 Larson, K.K. and Sarpong, R. (2009) *J. Am. Chem. Soc.*, **131**, 13244–13245.

240 Nakamura, H., Fujiawara, M., and Yamamoto, Y. (1998) *J. Org. Chem.*, **63**, 7529–7530.

241 Molander, G.A., Trice, S.L.J., and Dreher, S.D. (2010) *J. Am. Chem. Soc.*, **132**, 17701–17703.

242 Ishiyama, T., Ishida, K., and Miyaura, N. (2001) *Tetrahedron*, **57**, 9813–9816.

243 Billingsley, K.L. and Buchwald, S.L. (2008) *J. Org. Chem.*, **73**, 5589–5591.

244 Fürstner, A. and Seidel, G. (2002) *Org. Lett.*, **4**, 541–543.

245 Ma, Y., Song, C., Jiang, W., Xue, G., Cannon, J.F., Wang, X., and Andrus, M.B. (2003) *Org. Lett.*, **5**, 4635–4638.

246 Wilson, D.A., Wilson, C.J., Rosen, B.M., and Percec, V. (2008) *Org. Lett.*, **10**, 4879–4882.

247 Wilson, D.A., Wilson, C.J., Moldoveanu, C., Resmerita, A.-M., Corcoran, P., Hoang, L.M., Rosen, B.M., and Percec, V. (2010) *J. Am. Chem. Soc.*, **132**, 1800–1801.

248 (a) Zhu, W. and Ma, D. (2006) *Org. Lett.*, **8**, 261–263; (b) Kleeberg, C., Dang, L., Lin, Z., and Marder, T.B. (2009) *Angew. Chem., Int. Ed.*, **48**, 5350–5354.

249 Mkhalid, I.A.I., Barnard, J.H., Marder, T.B., Murphy, J.M., and Hartwig, J.F. (2010) *Chem. Rev.*, **110**, 890–931.

250 (a) Waltz, K.M. and Hartwig, J.F. (1997) *Science*, **277**, 211–213; (b) Chen, H. and Hartwig, J.F. (1999) *Angew. Chem., Int. Ed.*, **38**, 3391–3393.

251 (a) Iverson, C.N. and Smith, M.R., III (1999) *J. Am. Chem. Soc.*, **121**, 7696–7697; (b) Cho, J.-Y., Iverson, C.N., and Smith, M.R., III (2000) *J. Am. Chem. Soc.*, **122**, 12868–12869.

252 Chen, H., Schlecht, S., Temple, T.C., and Hartwig, J.F. (2000) *Science*, **287**, 1995–1997.

253 Ishiyama, T., Takagi, J., Ishida, K., Miyaura, N., Anastasi, N.R., and Hartwig, J.F. (2002) *J. Am. Chem. Soc.*, **124**, 390–391.

254 Shimada, S., Batsanov, A.S., Howard, J.A.K., and Marder, T.B. (2001) *Angew. Chem., Int. Ed.*, **40**, 2168–2171.

255 Chotana, G.A., Rak, M.A., and Smith, M.R., III (2005) *J. Am. Chem. Soc.*, **127**, 10539–10544.

256 Hurst, T.E., Macklin, T.K., Becker, M., Hartmann, E., Kugel, W., Parisienne-La Salle, J.C., Batsanov, A.S., Marder, T.B., and Snieckus, V. (2010) *Chem. Eur. J.*, **16**, 8155–8161.

257 Kawamorita, S., Ohmiya, H., Hara, K., Fukuoka, A., and Sawamura, M. (2009) *J. Am. Chem. Soc.*, **131**, 5058–5059.

258 Hilt, G. and Bolze, P. (2005) *Synthesis*, 2091–2115.

259 Moore, J.E., York, M., and Harrity, J.P.A. (2005) *Synlett*, 860–862.

260 Delaney, P.M., Browne, D.L., Adams, H., Plant, A., and Harrity, J.P.A. (2008) *Tetrahedron*, **64**, 866–873.

261 Davies, M.W., Johnson, C.N., and Harrity, J.P.A. (2001) *J. Org. Chem.*, **66**, 3525–3532.

262 (a) Yamamoto, Y., Ishii, J.-i., Nishiyama, H., and Itoh, K. (2004) *J. Am. Chem. Soc.*, **126**, 3712–3713; (b) Yamamoto, Y., Ishii, J.-i., Nishiyama, H., and Itoh, K. (2005) *Tetrahedron*, **61**, 11501–11510.

263 Auvinet, A.-L., Harrity, J.P.A., and Hilt, G. (2010) *J. Org. Chem.*, **75**, 3893–3896.

264 Mo, F.Y., Jiang, Y.B., Qiu, D., Zhang, Y., and Wang, J.B. (2010) *Angew. Chem., Int. Ed.*, **49**, 1846–1849.

265 Nielsen, D.R. and McEwen, W.E. (1957) *J. Am. Chem. Soc.*, **79**, 3081–3084.

266 Kaufman, D. (1987) *Chem. Ber.*, **120**, 901–905.

267 IJpeij, E.G., Beijer, F.H., Arts, H.J., Newton, C., de Vries, J.G., and Gruter, G.J.-M. (2002) *J. Org. Chem.*, **67**, 169–176.

268 Schilling, B., Kaiser, V., and Kaufmann, E.D. (1998) *Eur. J. Org. Chem.*, 701–709.

269 Tyrrell, E. and Brookes, P. (2004) *Synthesis*, 469–483.

270 Fuller, A.A., Hester, H.R., Salo, E.V., and Stevens, E.P. (2003) *Tetrahedron Lett.*, **44**, 2935–2938.

271 (a) Helm, M.D., Moore, J.E., Plant, A., and Harrity, J.P.A. (2005) *Angew. Chem., Int. Ed.*, **44**, 3889–3892; (b) Delaney, P.M., Huang, J., Macdonald, S.J.F., and Harrity, J.P.A. (2008) *Org. Lett.*, **10**, 781–783; (c) Huang, J., Macdonald, S.J.F., Cooper, A.W.J., Fisher, G., and Harrity, J.P.A. (2009) *Tetrahedron Lett.*, **50**, 5539–5541; (d) Browne, D.L., Vivat, J.F., Plant, A., Gomez-Bengoa, E., and Harrity, J.P.A. (2009) *J. Am. Chem. Soc.*, **131**, 7762–7769.

272 Dieck, H.A. and Heck, R.F. (1975) *J. Org. Chem.*, **40**, 1083–1090.

273 Brown, H.C. and Bhat, N.G. (1988) *Tetrahedron Lett.*, **29**, 21–24.

274 Uenishi, J., Matsui, K., and Wada, A. (2003) *Tetrahedron Lett.*, **44**, 3093–3096.

275 Matteson, D.S. (1960) *J. Am. Chem. Soc.*, **82**, 4228–4233.

276 Tivola, P.B., Deagostino, A., Prandi, C., and Venturello, P. (2002) *Org. Lett.*, **4**, 1275–1277.

277 Passafaro, M.S. and Keay, B.A. (1996) *Tetrahedron Lett.*, **37**, 429–432.

278 Rauniyar, V., Zhai, H.M., and Hall, D.G. (2008) *Synth. Commun.*, **38**, 3984–3995.

279 Gao, F. and Hoveyda, A.H. (2010) *J. Am. Chem. Soc.*, **132**, 10961–10963.

280 (a) Farinola, G.M., Fiandanese, V., Mazzone, L., and Naso, F. (1995) *J. Chem. Soc., Chem. Commun.*, 2523–2524; (b) Babudri, F., Farinola, G.M., Fiandanese, V., Mazzone, L., and Naso, F. (1998) *Tetrahedron*, **54**, 1085–1094.

281 Mikhail, I. and Kaufmann, D. (1990) *J. Organomet. Chem.*, **398**, 53–57.

282 Itami, K., Kamei, T., and Yoshida, J.-i. (2003) *J. Am. Chem. Soc.*, **125**, 14670–14671.

283 Cole, T.E., Quintanilla, R., and Rodewald, S. (1991) *Organometallics*, **10**, 3777–3781.

284 Takahashi, K., Takagi, J., Ishiyama, T., and Miyaura, N. (2000) *Chem. Lett.*, 126–127.

285 Takagi, J., Takahashi, K., Ishiyama, T., and Miyaura, N. (2002) *J. Am. Chem. Soc.*, **124**, 8001–8006.

286 Ishiyama, T., Takagi, J., Kamon, A., and Miyaura, N. (2003) *J. Organomet. Chem.*, **687**, 284–290.

287 Murata, M., Oyama, T., Watanabe, S., and Masuda, Y. (2000) *Synthesis*, 778–780.

288 Brown, H.C. and Subba Rao, B.C. (1956) *J. Am. Chem. Soc.*, **78**, 5694–5695.

289 Brown, H.C. (1962) *Hydroboration*, Benjamin, Reading MA.

290 Brown, H.C. and Zweifel, G. (1961) *J. Am. Chem. Soc.*, **83**, 3834–3840.

291 Zweifel, G. and Brown, H.C. (1963) *J. Am. Chem. Soc.*, **85**, 2066–2072.

292 Zweifel, G., Clark, G.M., and Polston, N.L. (1971) *J. Am. Chem. Soc.*, **93**, 3395–3399.

293 Brown, H.C., Scouten, C.G., and Liotta, R. (1979) *J. Am. Chem. Soc.*, **101**, 96–99.

294 Miyaura, N. and Suzuki, A. (1981) *Chem. Lett.*, 879–882.

295 Hoffman, R.W. and Dresely, S. (1988) *Synthesis*, 103–106.

296 Brown, H.C., Mandal, A.K., and Kulkarni, S.U. (1977) *J. Org. Chem.*, **42**, 1392–1398.

297 Martinez-Fresneda, P. and Vaultier, M. (1989) *Tetrahedron Lett.*, **30**, 2929–2932.

298 Kamabuchi, A., Moriya, T., Miyaura, N., and Suzuki, A. (1993) *Synth. Commun.*, **23**, 2851–2859.

299 Gravel, M., Touré, B.B., and Hall, D.G. (2004) *Org. Prep. Proced. Int.*, **36**, 573–580.

300 Kalinin, A.V., Scherer, S., and Snieckus, V. (2003) *Angew. Chem., Int. Ed.*, **42**, 3399–3404.

301 (a) Brown, H.C. and Gupta, S.K. (1972) *J. Am. Chem. Soc.*, **94**, 4370–4371; (b) Brown, H.C. and Gupta, S.K. (1975) *J. Am. Chem. Soc.*, **97**, 5249–5255; (c) Lane, C.F. and Kabalka, G.W. (1976) *Tetrahedron*, **32**, 981–990.

302 Arase, A., Hoshi, M., Mijin, A., and Nishi, K. (1995) *Synth. Commun.*, **25**, 1957–1962.

303 Scheidt, K.A., Tasaka, A., Bannister, T.D., Wendt, M.D., and Roush, W.R. (1999) *Angew. Chem., Int. Ed.*, **38**, 1652–1655.

304 Brown, H.C. and Campbell, J.B. (1980) *J. Org. Chem.*, **45**, 389–395.

305 Hassner, A. and Soderquist, J.A. (1977) *J. Organomet. Chem.*, **131**, C1–C4.

306 Soundararajan, R. and Matteson, D.S. (1990) *J. Org. Chem.*, **55**, 2274–2275.

307 Josyula, K.V.B., Gao, P., and Hewitt, C. (2003) *Tetrahedron Lett.*, **44**, 7789–7792.

308 Brown, H.C. and Imai, T. (1984) *Organometallics*, **3**, 1392–1395.

309 (a) Brown, H.C., Basavaiah, D., and Kulkarni, S.U. (1982) *J. Org. Chem.*, **47**, 3808–3810; (b) Brown, H.C., Imai, T., and Bhat, N.G. (1986) *J. Org. Chem.*, **51**, 5277–5282.

310 Hata, T., Kitagawa, H., Masai, H., Kurahashi, T., Shimizu, M., and Hiyama, T. (2001) *Angew. Chem., Int. Ed.*, **40**, 790–792.

311 Männig, D. and Nöth, H. (1985) *Angew. Chem., Int. Ed. Engl.*, **24**, 878–879.

312 (a) Burgess, K. and Ohlmeyer, M.J. (1991) *Chem. Rev.*, **91**, 1179–1191; (b) Beletskaya, I. and Pelter, A. (1997) *Tetrahedron*, **53**, 4957–5026.

313 He, X. and Hartwig, J.F. (1996) *J. Am. Chem. Soc.*, **118**, 1696–1702.

314 Pereira, S. and Srebnik, M. (1995) *Organometallics*, **14**, 3127–3128.

315 Wang, Y.D., Kimball, G., Prashad, A.S., and Wang, Y. (2005) *Tetrahedron Lett.*, **46**, 8777–8780.

316 Praveen Ganesh, N., d'Hondt, S., and Chavant, P.Y. (2007) *J. Org. Chem.*, **72**, 4510–4514.

317 Pereira, S. and Srebnik, M. (1996) *Tetrahedron Lett.*, **37**, 3283–3286.

318 Gridnev, I.D., Miyaura, N., and Suzuki, A. (1993) *Organometallics*, **12**, 589–592.

319 Lipshutz, B.H. and Bošković, Z.V. (2008) *Angew. Chem., Int. Ed.*, **47**, 10183–10186.

320 Satoh, M., Nomoto, Y., Miyaura, N., and Suzuki, A. (1989) *Tetrahedron Lett.*, **30**, 3789–3792.

321 Yamamoto, Y., Fujikawa, R., Yamada, A., and Miyaura, N. (1999) *Chem. Lett.*, 1069–1070.

322 Ohmura, T., Yamamoto, Y., and Miyaura, N. (2000) *J. Am. Chem. Soc.*, **122**, 4990–4991.

323 Gao, D. and O'Doherty, G.A. (2010) *Org. Lett.*, **12**, 3752–3755.

324 Renaud, J. and Ouellet, S.G. (1998) *J. Am. Chem. Soc.*, **120**, 7995–7996.

325 Connon, S.J. and Blechert, S. (2003) *Angew. Chem., Int. Ed.*, **42**, 1900–1923.

326 Blackwell, H.E., O'Leary, D.J., Chatterjee, A.K., Washenfelder, R.A., Bussmann, D.A., and Grubbs, R.H. (2000) *J. Am. Chem. Soc.*, **122**, 58–71.

327 Morrill, C. and Grubbs, R.H. (2003) *J. Org. Chem.*, **68**, 6031–6034.

328 Njardarson, J.T., Biswas, K., and Danishefsky, S.J. (2002) *Chem. Commun.*, 2759–2761.

329 (a) Renaud, J., Graf, C.-D., and Oberer, L. (2000) *Angew. Chem., Int. Ed.*, **39**, 3101–3104. (b) Micalizio, G.C. and Schreiber, S.L. (2002) *Angew. Chem., Int. Ed.*, **41**, 3272–3276.

330 Kim, M. and Lee, D. (2005) *Org. Lett.*, **7**, 1865–1868.

331 Coapes, B.R., Souza, F.E.S., Thomas, R.L., Hall, J.J., and Marder, T.B. (2003) *Chem. Commun.*, 614–615.

332 (a) Ishiyama, T., Matsuda, N., Miyaura, N., and Suzuki, A. (1993) *J. Am. Chem. Soc.*, **115**, 11018–11019; (b) Ishiyama, T., Matsuda, N., Murata, M., Ozawa, F., Suzuki, A., and Miyaura, N. (1996) *Organometallics*, **15**, 713–720.

333 (a) Iverson, C.N. and Smith, M.R. (1996) *Organometallics*, **15**, 5155–5165; (b) Lesley, M.J.G., Nguyen, P., Taylor, N.J., Marder, T.B., Scott, A.J., Clegg, W., and Norman, N.C. (1996) *Organometallics*, **15**, 5137–5154; (c) Anderson, K.M., Lesley, M.J.G., Norman, N.C., Orpen, A.G., and Starbuck, J. (1999) *New J. Chem.*, **23**, 1053–1055.

334 (a) Ishiyama, T., Yamamoto, M., and Miyaura, N. (1996) *Chem. Commun.*, 2073–2074; (b) Ishiyama, T., Kitano, T., and Miyaura, N. (1998) *Tetrahedron Lett.*, **39**, 2357–2360.

335 Takahashi, K., Ishiyama, T., and Miyaura, N. (2001) *J. Organomet. Chem.*, **625**, 47–53.

336 Lee, J.-E., Kwon, J., and Yun, J. (2008) *Chem. Commun.*, 733–734.

337 Suginome, M., Ohmura, T., Miyake, Y., Mitani, S., Ito, Y., and Murakami, M. (2003) *J. Am. Chem. Soc.*, **125**, 11174–11175.

338 Suginome, M., Yamamoto, A., and Murakami, M. (2003) *J. Am. Chem. Soc.*, **125**, 6358–6359.

339 Mannathan, S., Jeganmohan, M., and Cheng, C.-H. (2009) *Angew. Chem., Int. Ed.*, **48**, 2192–2195.

340 (a) Olsson, V.J. and Szabó, K.J. (2007) *Angew. Chem., Int. Ed.*, **46**, 6891–6893; (b) Olsson, V.J. and Szabó, K.J. (2009) *J. Org. Chem.*, **74**, 7715–7723.

341 Srebnik, M., Bhat, N.G., and Brown, H.C. (1988) *Tetrahedron Lett.*, **29**, 2635–2638.

342 Deloux, L. and Srebnik, M. (1994) *J. Org. Chem.*, **59**, 6871–6873.

343 Molander, G.A. and Ellis, N.M. (2008) *J. Org. Chem.*, **73**, 6841–6844.

344 (a) Hansen, E.C. and Lee, D. (2005) *J. Am. Chem. Soc.*, **127**, 3252–3253; (b) Suginome, M., Shirakura, M., and Yamamoto, A. (2006) *J. Am. Chem. Soc.*, **128**, 14438–14439; (c) Nishihara, Y., Miyasaka, M., Okamoto, M., Takahashi, H., Inoue, E., Tanemura, K., and Takagi, K. (2007) *J. Am. Chem. Soc.*, **129**, 12634–12635; (d) Geny, A., Leboeuf, D., Rouquié, G., Vollhardt, K.P.C., Malacria, M., Gandon, V., and Aubert, C. (2007) *Chem. Eur. J.*, **13**, 5408–5424.

345 Tonogaki, K., Itami, K., and Yoshida, J.-i. (2006) *J. Am. Chem. Soc.*, **128**, 1464–1465.

346 Shimizu, M., Kitagawa, H., Kurahashi, T., and Hiyama, T. (2001) *Angew. Chem., Int. Ed.*, **40**, 4283–4286.

347 Matteson, D.S. and Majumdar, D. (1983) *Organometallics*, **2**, 230–236.

348 Matteson, D.S., Moody, R.J., and Jesthi, P.K. (1975) *J. Am. Chem. Soc.*, **97**, 5608–5609.

349 Matteson, D.S. and Moody, R.J. (1982) *Organometallics*, **1**, 20–28.

350 Uenishi, J.-i., Beau, J.-M., Armstrong, R.W., and Kishi, Y. (1987) *J. Am. Chem. Soc.*, **109**, 4756–4758.

351 Evans, D.A., Ng, H.P., and Rieger, D.L. (1993) *J. Am. Chem. Soc.*, **115**, 11446–11459.

352 Endo, K., Hirokami, M., and Shibata, T. (2010) *J. Org. Chem.*, **75**, 3469–3472.

353 Takai, K., Shinomiya, N., Kaihara, H., Yoshida, N., and Moriwake, T. (1995) *Synlett*, 963–964.

354 Raheem, I.T., Goodman, S.N., and Jacobsen, E.N. (2004) *J. Am. Chem. Soc.*, **126**, 706–707.

355 Lightfoot, A.P., Maw, G., Thirsk, C., Twiddle, S.J.R., and Whiting, A. (2003) *Tetrahedron Lett.*, **44**, 7645–7648.

356 Heinrich, M.R., Sharp, L.A., and Zard, S.Z. (2005) *Chem. Commun.*, 3977–3079.

357 Satoh, Y., Serizawa, H., Miyaura, N., Hara, S., and Suzuki, A. (1988) *Tetrahedron Lett.*, **29**, 1811–1814.

358 Daini, M., Yamamoto, A., and Suginome, M. (2008) *J. Am. Chem. Soc.*, **130**, 2918–2919.

359 Carboni, B. (2005) Chapter 1, in *Boronic Acids*, 1st edn (ed. D.G. Hall), Wiley-VCH Verlag GmbH, Weinheim.

360 Matteson, D.S. and Peacock, K. (1963) *J. Org. Chem.*, **28**, 369–371.

361 Brown, H.C., Bhat, N.G., and Srebnik, M. (1988) *Tetrahedron Lett.*, **29**, 2631–2634.

362 Sato, M., Miyaura, N., and Suzuki, A. (1989) *Chem. Lett.*, 1405–1408.

363 (a) Rathke, M.W., Chao, E., and Wu, G. (1976) *J. Organomet. Chem.*, **122**, 145–149; (b) Wuts, P.G.M. and Thompson, P.A. (1982) *J. Organomet. Chem.*, **234**, 137–141; (c) Sadhu, K.M. and Matteson, D.S. (1985) *Organometallics*, **4**, 1687–1689.

364 Michnick, T.J. and Matteson, D.S. (1991) *Synlett*, 631–632.

365 (a) Matteson, D.S. and Majumdar, D. (1979) *J. Organomet. Chem.*, **170**, 259–264; (b) Phillion, D.P., Neubauer, R., and Andrew, S.S. (1986) *J. Org. Chem.*, **51**, 1610–1612.

366 Pintaric, C., Olivero, S., Gimbert, Y., Chavant, P.-Y., and Dunach, E. (2010) *J. Am. Chem. Soc.*, **132**, 11825–11827.

367 Brown, H.C. and Singaram, B. (1988) *Acc. Chem. Res.*, **21**, 287–293.

368 Brown, H.C. and Singaram, B. (1984) *J. Am. Chem. Soc.*, **106**, 1797–1800.

369 (a) Crudden, C.M. and Edwards, D. (2003) *Eur. J. Org. Chem.*, 4695–4712; (b) Carroll, A.-M., O'Sullivan, T.P., and Guiry, P.J. (2005) *Adv. Synth. Catal.*, **347**, 609–631.

370 (a) Smith, S.M. and Takacs, J.M. (2010) *J. Am. Chem. Soc.*, **132**, 1740–1741; (b) Smith, S.M. and Takacs, J.M. (2010) *Org. Lett.*, **12**, 4612–4615; Carroll, A.-M., O'Sullivan, T.P., and Guiry, P.J. (2005) *Adv. Synth. Catal.*, **347**, 609–631.

371 Lee, Y. and Hoveyda, A.H. (2009) *J. Am. Chem. Soc.*, **131**, 3160–3161.

372 Rubina, M., Rubin, M., and Gevorgyan, V. (2003) *J. Am. Chem. Soc.*, **125**, 7198–7199.

373 Hohn, E., Palecek, J., and Pietruszka, J. (2009) *Eur. J. Org. Chem.*, 3765–3782.

374 Hupe, E., Marek, I., and Knochel, P. (2002) *Org. Lett.*, **4**, 2861–2863.

375 (a) Ueda, M., Satoh, A., and Miyaura, N. (2002) *J. Organomet. Chem.*, **642**, 145–147; (b) Morgan, J.B. and Morken, J.P. (2004) *J. Am. Chem. Soc.*, **126**, 15338–15339; (c) Moran, M.J. and Morken, J.P. (2006) *Org. Lett.*, **8**, 2413–2415; (d) Paptchikhine, A., Cheruku, P., Engman, M., and Andersson, P.G. (2009) *Chem. Commun.*, 5996–5998.

376 Laitar, D.S., Tsui, E.Y., and Sadighi, J.P. (2006) *J. Am. Chem. Soc.*, **128**, 11036–11037.

377 (a) Burks, H.E. and Morken, J.P. (2007) *Chem. Commun.*, 4717–4718; (b) Kliman, L., Mlynarski, S.N., and Morken, J.P. (2009) *J. Am. Chem. Soc.*, **131**, 13210–13211.

378 Lee, Y., Jang, H., and Hoveyda, A.H. (2009) *J. Am. Chem. Soc.*, **131**, 18234–18235.

379 Sasaki, Y., Zhong, C.M., Sawamura, M., and Itoh, H. (2010) *J. Am. Chem. Soc.*, **132**, 1226–1227.

380 Schiffner, J.A., Müther, K., and Oestreich, M. (2010) *Angew. Chem., Int. Ed.*, **49**, 1194–1196.

381 (a) Mun, S., Lee, J.-E., and Yun, J. (2006) *Org. Lett.*, **8**, 4887–4889; (b) Lee, J.-E. and Yun, J. (2008) *Angew. Chem., Int. Ed.*, **47**, 145–147; (c) Sim, H.-S., Feng, X., and Yun, J. (2009) *Chem. Eur. J.*, **15**, 1939–1943; (d) Chea, H., Sim, H., and Yun, J. (2009) *Adv. Synth. Catal.*, **351**, 855–858; (e) Lillo, V., Prieto, A., Bonet, A., Díaz-Requejo, M.M., Ramírez, J., Pérez, P.J., and Fernández, E. (2009) *Organometallics*, **28**, 659–662; (f) Fleming, W.J., Müller-Bunz, H., Lillo, V., Fernández, E., and Guiry, P.J. (2009) *Org. Biomol. Chem.*, **7**, 2520–2524; (g) Lillo, V., Geier, M.J., Westcott, S.A., and Fernández, E. (2009) *Org. Biomol. Chem.*, **7**, 4674–4676; (h) Lee, Y. and Hoveyda, A.H. (2009) *J. Am. Chem. Soc.*, **131**, 3160–3161; (i) Chen, I.-H., Yin, L., Itano, W., Kanai, M., and Shibasaki, M. (2009) *J. Am. Chem. Soc.*, **131**, 11664–11665; (j) Shiomi, T., Adachi, T., Toribatake, K., Zhou, L., and Nishiyama, H. (2009) *Chem. Commun.*, 5987–5989.

382 (a) Lee, K.-S., Zhugralin, A.R., and Hoveyda, A.H. (2009) *J. Am. Chem. Soc.*, **131**, 7253–7255; (b) Bonet, A., Gulyás, H., and Fernández, E. (2010) *Angew. Chem., Int. Ed.*, **49**, 5130–5134.

383 Lee, J.C.H. and Hall, D.G. (2010) *J. Am. Chem. Soc.*, **132**, 5544–5545.

384 (a) Kennedy, J.W.J. and Hall, D.G. (2005) Chapter 6, in *Boronic Acids*, 1st edn (ed. D.G. Hall), Wiley-VCH Verlag GmbH, Weinheim; (b) Hall, D.G. (2008) *Pure Appl. Chem.*, **80**, 913–927.

385 (a) Carosi, L. and Hall, D.G. (2007) *Angew. Chem., Int. Ed.*, **27**, 5913–5915; (b) Lessard, S., Peng, F., and Hall, D.G. (2009) *J. Am. Chem. Soc.*, **131**, 9612–9613; (c) Guzman-Martinez, A. and Hoveyda, A.H. (2010) *J. Am. Chem. Soc.*, **132**, 10634–10637.

386 (a) Olsson, V.J., Sebelius, S., Selander, N., and Szabo, K.J. (2006) *J. Am. Chem. Soc.*, **128**, 4588–4589; (b) Selander, N., Kipke, A., Sebelius, S., and Szabo, K.J. (2007) *J. Am. Chem. Soc.*, **129**, 13723–13731. (c) Dutheuil, G., Selander, N., Szabo, K.J., Aggarwal, V.K. (2008) *Synthesis*, 2293–2297.

387 (a) Wu, J.Y., Moreau, B., and Ritter, T. (2009) *J. Am. Chem. Soc.*, **131**, 12915–12916; (b) Ely, R.J. and Morken, J.P. (2010) *J. Am. Chem. Soc.*, **132**, 2534–2535.

388 (a) Morin, C. (1994) *Tetrahedron*, **50**, 12521–12569; (b) Srebnik, M. (2003) *Tetrahedron*, **59**, 579–593.

389 Laplante, C. and Hall, D.G. (2001) *Org. Lett.*, **3**, 1487–1490.

390 Matteson, D.S. and Liedtke, J.D. (1965) *J. Am. Chem. Soc.*, **87**, 1526–1531.

391 Matteson, D.S. (1999) *J. Organomet. Chem.*, **581**, 51–65.

392 Mothana, S., Grassot, J.-M., and Hall, D.G. (2010) *Angew. Chem., Int. Ed.*, **49**, 2883–2887.

393 Michaelis, A. (1901) *Justus Liebigs Ann. Chem.*, **315**, 19.

394 Zhong, Z. and Anslyn, E.V. (2002) *J. Am. Chem. Soc.*, **124**, 9014–9015.

395 Cai, S.X. and Keana, J.F.W. (1991) *Bioconjug. Chem.*, **2**, 317–322.

396 (a) Matteson, D.S. and Arne, K.H. (1978) *J. Am. Chem. Soc.*, **100**, 1325–1326; (b) Matteson, D.S. and Arne, K.H. (1982) *Organometallics*, **1**, 280–288.

397 Matteson, D.S. and Majumdar, D. (1980) *J. Chem. Soc., Chem. Commun.*, 39–40.

398 Jagannathan, S., Forsyth, T.P., and Kettner, C.A. (2001) *J. Org. Chem.*, **66**, 6375–6380.

399 Matteson, D.S. and Moody, R.J. (1980) *J. Org. Chem.*, **45**, 1091–1095.

400 Matteson, D.S. (1975) *Synthesis*, 147–158.

401 Endo, K., Hirokami, M., and Shibata, T. (2009) *Synlett*, 1131–1135.

402 Matteson, D.S. and Wilson, J.W. (1985) *Organometallics*, **4**, 1690–1692.

403 (a) Knochel, P. (1990) *J. Am. Chem. Soc.*, **112**, 7431–7433; (b) Sakai, M., Saito, S., Kanai, G., Suzuki, A., and Miyaura, N. (1996) *Tetrahedron Lett.*, **52**, 915–924.

404 Waas, J.R., Sidduri, A., and Knochel, P. (1992) *Tetrahedron Lett.*, **33**, 3717–3720.

405 Brown, H.C. and Imai, T. (1983) *J. Am. Chem. Soc.*, **105**, 6285–6289.

406 (a) Matteson, D.S. (1988) *Tetrahedron*, **54**, 10555–10607; (b) Matteson, D.S. (2005) Chapter 8, in *Boronic Acids*, 1st edn (ed. D.G. Hall), Wiley-VCH Verlag GmbH, Weinheim.

407 Wityak, J., Earl, R.A., Abelman, M.M., Bethel, Y.B., Fisher, B.N., Kauffman, G.K., Kettner, C.A., Ma, P., McMillan, J.L., Mersinger, L.J., Pesti, J., Pierce, M.E., Rankin, F.W., Chorvat, R.J., and Confalone, P.N. (1995) *J. Org. Chem.*, **60**, 3717–3722.

408 Thomas, S.P., French, R.M., Jheengut, V., and Aggarwal, V.K. (2009) *Chem. Rec.*, **9**, 24–39.

409 Ni, W., Fang, H., Springsteen, G., and Wang, B. (2004) *J. Org. Chem.*, **69**, 1999–2007.

410 Kuivila, H.G., Benjamin, L.E., Murphy, C.J., Price, A.D., and Polevy, J.H. (1962) *J. Org. Chem.*, **27**, 825–829.

411 Al-Zoubi, R.M. and Hall, D.G. (2010) *Org. Lett.*, **12**, 2480–2483.

412 Qiu, D., Mo, F., Zheng, Z., Zhang, Y., and Wang, J. (2010) *Org. Lett.*, **12**, 5474–5477.

413 Dai, C., Li, M. and Wang, B. (2009) *Chem. Commun.*, 5251–5253.

414 Gilman, H., Swayampati, D.R., and Ranck, R.O. (1958) *J. Am. Chem. Soc.*, **80**, 1355–1357.

415 Baron, O. and Knochel, P. (2005) *Angew. Chem., Int. Ed.*, **44**, 3133–3135.

416 Lopes-Ruiz, H. and Zard, S.Z. (2001) *Chem. Commun.*, 2618–2619.

417 Moriya, T., Suzuki, A., and Miyaura, N. (1995) *Tetrahedron Lett.*, **36**, 1887–1888.

418 (a) Rasset-Deloge, C., Martinez-Fresneda, P., and Vaultier, M. (1992) *Bull. Soc. Chim. Fr.*, **129**, 285–290; (b) Jehanno, E. and Vaultier, M. (1995) *Tetrahedron Lett.*, **36**, 4439–4442. (c) Châtaigner, I., Lebreton, J., Zammatio, F., and Villiéras, J. (1997) *Tetrahedron Lett.* **38**, 3719–3722.

419 Andrade, L.H. and Barcellos, T. (2009) *Org. Lett.*, **11**, 3052–3055.

420 Kinder, D.H. and Ames, M.M. (1987) *J. Org. Chem.*, **52**, 2452–2454.

421 Curtis, A.D.M. and Whiting, A. (1991) *Tetrahedron Lett.*, **32**, 1507–1510.

422 Chan, K.-F. and Wong, H.N.C. (2001) *Org. Lett.*, **3**, 3991–3994.

423 (a) Yamamoto, Y., Seko, T., and Nemoto, H. (1989) *J. Org. Chem.*, **54**, 4734–4736; (b) Vedsø, P., Olesen, P.H., and Hoeg-Jensen, T. (2004) *Synlett*, 892–894; (c) Dabrowski, M., Kurach, P., Lulinski, S., and Serwatowski, J. (2007) *Appl. Organomet. Chem.*, **21**, 234–238.

424 Durka, K., Kurach, P., Lulinski, S., and Serwatowski, J. (2009) *Eur. J. Org. Chem.*, 4325–4332.

425 Gillis, E.P. and Burke, M.D. (2008) *J. Am. Chem. Soc.*, **130**, 14084–14085.

426 (a) Lee, S.J., Gray, K.G., Paek, J.S., and Burke, M.D. (2008) *J. Am. Chem. Soc.*, **130**, 466–468; (b) Lee, S.J., Anderson, T.M., and Burke, M.D. (2010) *Angew. Chem., Int. Ed.*, **49**, 8860–8863.

427 Noguchi, H., Shioda, T., Chou, C.-M., and Suginome, M. (2008) *Org. Lett.*, **10**, 377–380.

428 Ihara, H. and Suginome, M. (2009) *J. Am. Chem. Soc.*, **131**, 7502–7503.

429 Santucci, L. and Gilman, H. (1958) *J. Am. Chem. Soc.*, **80**, 193–196.

430 Cao, H., McGill, T., and Heagy, M.D. (2004) *J. Org. Chem.*, **69**, 2959–2966.

431 (a) Hall, D.G., Tailor, J., and Gravel, M. (1999) *Angew. Chem., Int. Ed.*, **38**, 3064–3067; (b) Arimori, S., Hartley, J.H., Bell, M.L., Oh, C.S., and James, T.D. (2000) *Tetrahedron Lett.*, **41**, 10291–10294.

432 Gravel, M., Thompson, K.A., Zak, M., Bérubé, C., and Hall, D.G. (2002) *J. Org. Chem.*, **67**, 3–15.

433 Tsukamoto, H., Suzuki, T., Sato, M., and Kondo, Y. (2007) *Tetrahedron Lett.*, **48**, 8438–8441.

434 Gravel, M., Bérubé, C., and Hall, D.G. (2000) *J. Comb. Chem.*, **2**, 228–231.

435 Thompson, K.A. and Hall, D.G. (2000) *Chem. Commun.*, 2379–2380.

436 Carboni, B., Pourbaix, C., Carreaux, F., Deleuze, H., and Maillard, B. (1999) *Tetrahedron Lett.*, **40**, 7979–7983.

437 Pourbaix, C., Carreaux, F., and Carboni, B. (2001) *Org. Lett.*, **3**, 803–805.

438 Pourbaix, C., Carreaux, F., Carboni, B., and Deleuze, H. (2000) *Chem. Commun.*, 1275–1276.

439 (a) Li, W. and Burgess, K. (1999) *Tetrahedron Lett.*, **40**, 6527–6530; (b) Dunsdon, R.M., Greening, J.R., Jones, P.S., Jordan, S., and Wilson, F.X. (2000) *Bioorg. Med. Chem. Lett.*, **10**, 1577–1579.

440 Arnauld, T., Barrett, A.G.M., and Seifried, R. (2001) *Tetrahedron Lett.*, **42**, 7889–7901.

441 Wang, W.Q., Gao, X.M., Springsteen, G., and Wang, B. (2002) *Tetrahedron Lett.*, **43**, 6339–6342.

442 (a) Chen, D., Qing, F.-L., and Huang, Y. (2002) *Org. Lett.*, **4**, 1003–1006; (b) Huang, Y., Chen, D., and Qing, F.L. (2003) *Tetrahedron*, **59**, 7879–7886.

443 Hebel, A. and Haag, R. (2002) *J. Org. Chem.*, **67**, 9452–9455.

444 Dennis, L.M. and Shelton, R.S. (1930) *J. Am. Chem. Soc.*, **52**, 3128–3132.

445 Gilman, H., Santucci, L., Swayampati, D.R., and Ranck, R.O. (1957) *J. Am. Chem. Soc.*, **79**, 2898–2901.

446 Duran, D., Wu, N., Mao, B., and Xu, J. (2006) *J. Liq. Chromatogr. Relat. Technol.*, **29**, 661–672.

447 Longstaff, C. and Rose, M.E. (1982) *Org. Mass Spectrom.*, **17**, 508–518.

448 Kaminski, J.J. and Lyle, R.E. (1978) *Org. Mass Spectrom.*, **13**, 425–428.

449 Haas, M.J., Blom, K.F., and Schwarz, C.H., III (1999) *Anal. Chem.*, **71**, 1574–1578.

450 Hermánek, S. (1992) *Chem. Rev.*, **92**, 325–362.

451 Nöth, H. and Wrackmeyer, B. (1978) *Nuclear Magnetic Resonance Spectroscopy of Boron Compounds*, NMR Basic Principles and Progress Series 14 (eds P. Diehl, E. Fluck, and R. Kosfeld), Springer, Berlin.

452 Matteson, D.S. and Krämer, E. (1968) *J. Am. Chem. Soc.*, **90**, 7261–7267.

453 Larock, R.C., Gupta, S.K., and Brown, H.C. (1972) *J. Am. Chem. Soc.*, **94**, 4371–4373.

454 Rozema, M.J., Rajagopal, D., Tucker, C.E., and Knochel, P. (1992) *J. Organomet. Chem.*, **438**, 11–27.

455 Challenger, F. and Parker, B. (1931) *J. Chem. Soc.*, 1462–1467.

456 Kuivila, H.G., Reuwer, J.F., and Mangravite, J.A. (1964) *J. Am. Chem. Soc.*, **86**, 2666–2670.

457 (a) Bolm, C. and Rudolph, J. (2003) *J. Am. Chem. Soc.*, **125**, 14850–14851; (b) Jimeno, C., Sayalero, S., Fjermestad, T., Colet, G., Maseras, F., and Pericàs, M.A. (2008) *Angew. Chem., Int. Ed.*, **47**, 1098–1101; (c) Fandrick, D.R., Fandrick, K.R., Reeves, J.T., Tan, Z., Johnson, C.S., Lee, H., Song, J.J., Yee, N.K., and Senanayake, C.H. (2010) *Org. Lett.*, **12**, 88–91; (d) Fandrick, K.R., Fandrick, D.R., Gao, J.J., Reeves, J.T., Tan, Z.L., Li, W.J., Song, J.H.J., Lu, B., Yee, N.K., and Senanayake, C.H. (2010) *Org. Lett.*, **12**, 3748–3751.

458 Matano, Y., Begum, S.A., Miyamatsu, T., and Suzuki, H. (1998) *Organometallics*, **17**, 4332–4334.

459 (a) Partyka, D.V., Zeller, M., Hunter, A.D., and Gray, T.G. (2006) *Angew. Chem., Int. Ed.*, **45**, 8188–8191; (b) Seidel, G., Lehmann, C.W., and Fürstner, A. (2010) *Angew. Chem., Int. Ed.*, **49**, 8466–8470.

460 Klingensmith, L.M., Bio, M.M., and Moniz, G.A. (2007) *Tetrahedron Lett.*, **48**, 8242–8245.

461 Brown, H.C. and Zweifel, G. (1961) *J. Am. Chem. Soc.*, **83**, 2544–2551.

462 Maleczka, R.E., Jr., Shi, F., Holmes, D., and Smith, M.R., III (2003) *J. Am. Chem. Soc.*, **125**, 7792–7793.

463 (a) Kuivila, H.G. (1954) *J. Am. Chem. Soc.*, **76**, 870–874; (b) Kuivila, H.G. and Armour, A.G. (1957) *J. Am. Chem. Soc.*, **79**, 5659–5662.

464 Kabalka, G.W. and Hedgecock, H.C., Jr. (1975) *J. Org. Chem.*, **40**, 1776–1779.

465 Webb, K.S. and Levy, D. (1995) *Tetrahedron Lett.*, **36**, 5117–5118.

466 (a) Matteson, D.S. and Ray, R. (1980) *J. Am. Chem. Soc.*, **102**, 7591–7593; (b) Fontani, P., Carboni, B., Vaultier, M., and Maas, G. (1991) *Synthesis*, 605–609.

467 Kianmehr, E., Yahyaee, M., and Tabatabai, K. (2007) *Tetrahedron Lett.*, **48**, 2713–2715.

468 (a) Prakash, G.K.S., Chacko, S., Panja, C., Thomas, T.E., Gurung, L., Rasul, G., Mathew, T., and Olah, G.A. (2009) *Adv. Synth. Catal.*, **351**, 1567–1574; (b) Xu, J., Wang, X., Shao, C., Su, D., Cheng, G., and Hu, Y. (2010) *Org. Lett.*, **12**, 1964–1967.

469 Kyne, R.E., Ryan, M.C., Kliman, L.T., and Morken, J.P. (2010) *Org. Lett.*, **12**, 3796–3799.

470 Murata, M., Satoh, K., Watanabe, S., and Masuda, Y. (1998) *J. Chem. Soc., Perkin Trans.* **1**, 1465–1466.

471 Huber, M.-L. and Pinhey, J.T. (1990) *J. Chem. Soc., Perkin Trans.* **1**, 721–722.

472 (a) Stefan, S., Jurgen, S., Prakash, G.K.S., Petasis, N.A., and Olah, G.A. (2000) *Synlett*, 1845–1847; (b) Prakash, G.K.S., Panja, C., Mathew, T., Surampudi, V., Petasis, N.A., and Olah, G.A. (2004) *Org. Lett.*, **6**, 2205–2207.

473 Brown, H.C., Kim, K.-W., Cole, T.E., and Singaram, B. (1986) *J. Am. Chem. Soc.*, **108**, 6761–6764.

474 (a) Jego, J.-M., Carboni, B., Vaultier, M., and Carrié, R. (1989) *J. Chem. Soc., Chem. Commun.*, 142–143; (b) Jego, J.-M., Carboni, B., and Vaultier, M. (1992) *Bull. Soc. Chim. Fr.*, **129**, 554–565.

475 Rao, H., Fu, H., Jiang, Y., and Zhao, Y. (2009) *Angew. Chem., Int. Ed.*, **48**, 1114–1116; Jiang, Z.Q., Wu, Z.Q., Wang, L.X., Wu, D., and Zhou, X.G. (2010) *Can. J. Chem.*, **88**, 964–968.

476 Yu, Y., Srogl, J., and Liebeskind, L.S. (2004) *Org. Lett.*, **6**, 2631–2634.

477 Prakash, G.K.S., Moran, M.D., Mathew, T., and Olah, G.A. (2009) *J. Fluor. Chem.*, **130**, 806–809.

478 Murphy, J.C., Liao, X., and Hartwig, J.F. (2007) *J. Am. Chem. Soc.*, **129**, 15434–15435.

479 Kuivila, H.G. and Easterbrook, E.K. (1951) *J. Am. Chem. Soc.*, **73**, 4629–4632.

480 Kuivila, H.G. and Hendrickson, A.R. (1952) *J. Am. Chem. Soc.*, **74**, 5068–5070.

481 Thiebes, C., Prakash, G.K.S., Petasis, N.A., and Olah, G.A. (1998) *Synlett*, 141–142.

482 Szumigala, R.H., Jr., Devine, P.N., Gauthier, D.R., Jr., and Volante, R.P. (2004) *J. Org. Chem.*, **69**, 566–569.

483 Thompson, A.L.S., Kabalka, G.W., Akula, M.R., and Huffman, J.W. (2005) *Synthesis*, 547–550.

484 Yao, M.-L., Reddy, M.S., Yong, L., Walfish, I., Blevins, D.W., and Kabalka, G.W. (2010) *Org. Lett.*, **12**, 700–703.

485 (a) Diorazio, L.J., Widdowson, D.A., and Clough, J.M. (1992) *Tetrahedron*, **48**, 8073–8088; (b) Clough, J.M., Diorazio, L.J., and Widdowson, D.A. (1990) *Synlett*, 761–762.

486 Furuya, T., Kaiser, H.M., and Ritter, T. (2008) *Angew. Chem., Int. Ed.*, **47**, 5993–5996.

487 Furuya, T. and Ritter, T. (2009) *Org. Lett.*, **11**, 2860–2863.

488 Carroll, M.A., Pike, V.W., and Widdowson, D.A. (2000) *Tetrahedron Lett.*, **41**, 5393–5396.

489 Brown, H.C., Hamaoka, T., and Ravindran, N. (1973) *J. Am. Chem. Soc.*, **95**, 6456–6457.

490 Brown, H.C., Bhat, N.G., and Rajagopalan, S. (1986) *Synthesis*, 480–482.

491 Brown, H.C., Subrahmanyam, C., Hamaoka, T., Ravindran, N., Bowman, D.H., Misumi, S., Unni, M.K., Somayaji, V., and Bhat, N.G. (1989) *J. Org. Chem.*, **54**, 6068–6075.

492 (a) Brown, H.C., Hamaoka, T., and Ravindran, N. (1973) *J. Am. Chem. Soc.*, **95**, 5786–5788; (b) Brown, H.C. and Somayaji, V. (1984) *Synthesis*, 919–920; (c) Brown, H.C., Hamaoka, T.,

Ravindran, N., Subrahmanyam, C., Somayaji, V., and Bhat, N.G. (1989) *J. Org. Chem.*, **54**, 6075–6079.

493 Kabalka, G.W., Gooch, E.E., and Hsu, H.C. (1981) *Synth. Commun.*, **11**, 247–251.

494 (a) Stewart, S.K. and Whiting, A. (1995) *Tetrahedron Lett.*, **36**, 3929–3932; (b) Henaff, N., Stewart, S. K., Whiting, A. (1997) *Tetrahedron Lett.* **38**, 4525–4526.

495 Petasis, N.A. and Zavialov, I.A. (1996) *Tetrahedron Lett.*, **37**, 567–570.

496 Kunda, S.A., Smith, T.L., Hylarides, M.D., and Kabalka, G.W. (1985) *Tetrahedron Lett.*, **26**, 279–280.

497 Miyaura, N. and Suzuki, A. (1979) *J. Chem. Soc., Chem. Commun.*, 866–867.

498 Miyaura, N., Yanagi, T., and Suzuki, A. (1981) *Synth. Commun.*, **11**, 513–519.

499 (a) Miyaura, N. and Suzuki, A. (1995) *Chem. Rev.*, **95**, 2457–2483; (b) Suzuki, A. (1999) *J. Organomet. Chem.*, **576**, 147–168; (c) Miyaura, N. (2002) *Top. Curr. Chem.*, **219**, 11–59; (d) Kotha, S., Lahiri, K., and Kashinath, D. (2002) *Tetrahedron*, **58**, 9633–9695; (e) Hassan, J., Sévignon, M., Gozzi, C., Schulz, E., and Lemaire, M. (2002) *Chem. Rev.*, **102**, 1359–1469; (f) Suzuki, A. (2004) *Proc. Jpn Acad., Ser. B*, **80**, 359–371; (g) Nicolaou, K.C., Bulger, P.G., and Sarlah, D. (2005) *Angew. Chem., Int. Ed.*, **44**, 4442–4489.

500 Miyaura, N., Yamada, K., Suginome, H., and Suzuki, A. (1985) *J. Am. Chem. Soc.*, **107**, 972–980.

501 Smith, G.B., Dezeny, G.C., Hughes, D.L., King, A.O., and Verhoeven, T.R. (1994) *J. Org. Chem.*, **59**, 8151–8156.

502 Moreno-Manas, M., Pérez, M., and Pleixats, R. (1996) *J. Org. Chem.*, **61**, 2346–2351.

503 Aliprantis, A.O. and Canary, J.W. (1994) *J. Am. Chem. Soc.*, **116**, 6985–6986.

504 Miyaura, N. (2002) *J. Organomet. Chem.*, **653**, 54–57.

505 (a) Martin, A.R. and Yang, Y. (1993) *Acta. Chem. Scand.*, **47**, 221–230; (b) Matos, K. and Soderquist, J.A. (1998) *J. Org. Chem.*, **63**, 461–470; (c) Braga, A.A.C., Morgon, N.H., Ujaque, G., Lledos, A., and Maseras, F. (2005) *J. Am. Chem. Soc.*, **127**, 9288–9307; (d) Braga, A.A.C., Morgon, N.H., Ujaque, G., Lledos, A., and Maseras, F. (2006) *J. Organomet. Chem.*, **691**, 4459–4466.

506 Carrow, B.P. and Hartwig, J.F. (2011) *J. Am. Chem. Soc.*, **133**, 2116–2119.

507 (a) Ishiyama, T., Kizaki, H., Miyaura, N., and Suzuki, A. (1993) *Tetrahedron Lett.*, **34**, 7595–7598; (b) Ishiyama, T., Kizaki, H., Hayashi, T., Suzuki, A., and Miyaura, N. (1998) *J. Org. Chem.*, **63**, 4726–4731.

508 (a) Bumagin, N.A. and Korolev, D.N. (1999) *Tetrahedron Lett.*, **40**, 3057–3060; (b) Haddach, M. and McCarthy, J.R. (1999) *Tetrahedron Lett.*, **40**, 3109–3112.

509 Goossen, L.J. and Ghosh, K. (2001) *Angew. Chem., Int. Ed.*, **40**, 3458–3460.

510 Barder, T.E. and Buchwald, S.L. (2007) *Org. Lett.*, **9**, 137–139.

511 (a) Gronowitz, S., Hörnfeldt, A.-B., and Yang, Y.-H. (1986) *Chem. Scr.*, **26**, 383–386; (b) Chaumeil, H., Signorella, S., and Le Drian, C. (2000) *Tetrahedron*, **56**, 9655–9662.

512 Wright, S.W., Hageman, D.L., and McClure, L.D. (1994) *J. Org. Chem.*, **59**, 6095–6097.

513 Watanabe, T., Miyaura, N., and Suzuki, A. (1992) *Synlett*, 207–209.

514 Yoshida, H., Yamaryo, Y., Ohshita, J., and Kunai, A. (2003) *Tetrahedron Lett.*, **44**, 1541–1544.

515 Cai, X. and Snieckus, V. (2004) *Org. Lett.*, **6**, 2293–2295.

516 (a) Kerins, F. and O'Shea, D.F. (2002) *J. Org. Chem.*, **67**, 4968–4971; (b) Lightfoot, A.P., Twiddle, S.J.R., and Whiting, A. (2005) *Synlett*, 529–531.

517 (a) Miyaura, N., Suginome, H., and Suzuki, A. (1983) *Tetrahedron*, **39**, 3271–3277; (b) Miyaura, N. and Suzuki, A. (1990) *Org. Synth.*, **68**, 130–136.

518 Roush, W.R., Reilly, M.L., Koyama, K., and Brown, B.B. (1997) *J. Org. Chem.*, **62**, 8708–8721.

519 Sebelius, S., Olsson, V.J., Wallner, O.A., and Szabo, K.J. (2006) *J. Am. Chem. Soc.*, **128**, 8150–8151.

520 (a) Chemler, S.R., Trauner, D., and Danishefsky, S.J. (2001) *Angew. Chem., Int. Ed.*, **40**, 4544–4568, and references

cited therein; (b) Zou, G., Reddy, Y.K., and Falck, J.R. (2001) *Tetrahedron Lett.*, **42**, 7213–7215; (c) Kataoka, N., Shelby, Q., Stambuli, J.P., and Hartwig, J.F. (2002) *J. Org. Chem.*, **67**, 5553–5566; (d) Zhou, S.-M., Deng, M.-Z., Xia, L.-J., and Tang, M.-H. (1998) *Angew. Chem., Int. Ed.*, **37**, 2845–2847.

521 Doucet, H. (2008) *Eur. J. Org. Chem.*, 2013–2030.

522 Gonzalez-Bobes, F. and Fu, G.C. (2006) *J. Am. Chem. Soc.*, **128**, 5360–5361.

523 Kirchhoff, J.H., Netherton, M.R., Hills, I.D., and Fu, G.C. (2002) *J. Am. Chem. Soc.*, **124**, 13662–13663.

524 (a) Crudden, C.M., Glasspoole, B.W., and Lata, C.J. (2009) *Chem. Commun.*, 6704–6716; (b) Imao, D., Glaspoole, B.W., Laberge, V.S., and Crudden, C.M. (2009) *J. Am. Chem. Soc.*, **131**, 5024–5025; (c) He, A. and Falck, J.R. (2010) *J. Am. Chem. Soc.*, **132**, 2524–2525; (d) Ohmura, T., Awano, T., and Suginome, M. (2010) *J. Am. Chem. Soc.*, **132**, 13191–13193; (e) Sandrock, D.L., Jean-Gérard, L., Chen, C.Y., and Dreher, S.D. (2010) *J. Am. Chem. Soc.*, **132**, 17108–17110.

525 Sakamoto, J., Rehahn, M., Wegner, G., and Schluter, A.D. (2009) *Macromol. Rapid Commun.*, **30**, 653–687.

526 (a) Franzen, R. (2000) *Can. J. Chem.*, **78**, 957–962; (b) Brase, S., Kirchhoff, J.H., and Kobberling, J. (2003) *Tetrahedron*, **59**, 885–939.

527 (a) Urawa, Y., Naka, H., Miyazawa, M., Souda, S., and Ogura, K. (2002) *J. Organomet. Chem.*, **653**, 269–278; (b) Yasuda, N. (2002) *J. Organomet. Chem.*, **653**, 279–287.

528 Littke, A.F. and Fu, G.C. (2002) *Angew. Chem., Int. Ed.*, **41**, 4176–4211.

529 (a) Littke, A.F. and Fu, G.C. (1998) *Angew. Chem., Int. Ed.*, **37**, 3387–3388; (b) Littke, A.F., Dai, C., and Fu, G.C. (2000) *J. Am. Chem. Soc.*, **122**, 4020–4028; (c) Review: Fu, G.C. (2008) *Acc. Chem. Res.*, **41**, 1555–1564.

530 (a) Old, D.W., Wolfe, J.P., and Buchwald, S.L. (1998) *J. Am. Chem. Soc.*, **120**, 9722–9723; (b) Wolfe, J.P., Singer, R.A., Yang, B.H., and Buchwald, S.L. (1999) *J. Am. Chem. Soc.*, **121**, 9550–9561; (c) Yin, J., Rainka, M.P., Zhang, X.-X., and Buchwald, S.L. (2002) *J. Am. Chem. Soc.*, **124**, 1162–1163; (d) Billingsley, K. and Buchwald, S.L. (2007) *J. Am. Chem. Soc.*, **129**, 3358–3366; (e) Martin, R. and Buchwald, S.L. (2008) *Acc. Chem. Res.*, **41**, 1461–1473.

531 O'Brien, C.J., Kantchev, E.A.B., Valente, C., Hadei, N., Chass, G.A., Lough, A., Hopkinson, A.C., and Organ, M.E. (2006) *Chem. Eur. J.*, **12**, 4743–4778.

532 (a) Gstottmayr, C.W.K., Bohn, V.P.M., Herdtweck, E., Grosche, M., and Hermann, W.A. (2002) *Angew. Chem., Int. Ed.*, **41**, 1363–1365; (b) Stambuli, J.P., Kuwano, R., and Hartwig, J.F. (2002) *Angew. Chem., Int. Ed.*, **41**, 4746–4748.

533 Walker, S.D., Barder, T.E., Martinelli, J.R., and Buchwald, S.L. (2004) *Angew. Chem., Int. Ed.*, **43**, 1871–1876.

534 Navarro, O., Kelly, R.A., III, and Nolan, S.P. (2003) *J. Am. Chem. Soc.*, **125**, 16194–16195.

535 Percec, V., Bae, J.-Y., and Hill, D.H. (1995) *J. Org. Chem.*, **60**, 1060–1065.

536 Na, Y., Park, S., Han, S.B., Han, H., Ko, S., and Chang, S. (2004) *J. Am. Chem. Soc.*, **126**, 250–258.

537 (a) Guo, Y., Young, D.J., and Hot, T.S.A. (2008) *Tetrahedron Lett.*, **49**, 5620–5621; (b) Hatakeyama, T., Hashimoto, T., Kondo, Y., Fujiwara, Y., Seike, H., Takaya, H., Tamada, Y., Ono, T., and Nakamura, M. (2010) *J. Am. Chem. Soc.*, **132**, 10674–10676.

538 (a) González-Arellano, C., Corma, A., Iglesias, M., and Sánchez, F. (2006) *J. Catal.*, **238**, 497–501; (b) Mankad, N.P. and Toste, F.D. (2010) *J. Am. Chem. Soc.*, **132**, 12859–12861.

539 Sakurai, H., Tsukuda, T., and Hirao, T. (2002) *J. Org. Chem.*, **67**, 2721–2722, and references cited therein.

540 Leadbeater, N.E. and Marco, M. (2003) *J. Org. Chem.*, **68**, 5660–5667. A reassessment of this procedure revealed that minute levels of Pd contaminants in the inorganic base employed are responsible for the generation of biaryl products: Arvela, R. K., Leadbeater, N. E., Sangi, M. S.,

Williams, V.A., Granados, P., and Singer, R. D. (2005) *J. Org. Chem.* **70**, 161–168.
541 Schaub, T., Backes, M., and Radius, U. (2006) *J. Am. Chem. Soc.*, **128**, 15964–15965.
542 (a) Nguyen, H.N., Huang, X., and Buchwald, S.L. (2003) *J. Am. Chem. Soc.*, **125**, 11818–11819; (b) Percec, V., Golding, G.M., Smidrkal, J., and Weichold, O. (2004) *J. Org. Chem.*, **69**, 3447–3452; (c) Ang, Z.-Y. and Hu, Q.-S. (2004) *J. Am. Chem. Soc.*, **126**, 3058–3059.
543 Blakey, S.B. and MacMillan, D.W.C. (2003) *J. Am. Chem. Soc.*, **125**, 6046–6047.
544 (a) Quasdorf, K.W., Tian, X., and Garg, N.K. (2008) *J. Am. Chem. Soc.*, **130**, 14422–14423; (b) Guan, B.-T., Wang, Y., Li, B.-J., Yu, D.-G., and Shi, Z.-J. (2008) *J. Am. Chem. Soc.*, **130**, 14468–14470; (c) Quasdorf, K.W., Riener, M., Petrova, K.V., and Garg, N.K. (2009) *J. Am. Chem. Soc.*, **131**, 17748–17749.
545 Tobisu, M., Shimasaki, T., and Chatani, N. (2008) *Angew. Chem., Int. Ed.*, **47**, 4866–4869.
546 (a) Ohmiya, H., Makida, Y., Li, D., Tanabe, M., and Sawamura, M. (2010) *J. Am. Chem. Soc.*, **132**, 879–889; (b) Pigge, F.C. (2010) *Synthesis*, 1745–1762.
547 Nishikata, T. and Lipshutz, B.H. (2009) *J. Am. Chem. Soc.*, **131**, 12103–12105.
548 (a) Tsukamoto, H., Sato, M., and Kondo, Y. (2004) *Chem. Commun.*, 1200–1201; (b) Kayaki, Y., Koda, T., and Ikariya, T. (2004) *Eur. J. Org. Chem.*, 4989–4993; (c) Yoshida, M., Gotou, T., and Ihara, M. (2004) *Tetrahedron Lett.*, **45**, 5573–5575.
549 Srogl, J., Allred, G.D., and Liebeskind, L.S. (1997) *J. Am. Chem. Soc.*, **119**, 12376–12377.
550 (a) Savarin, C., Srogl, J., and Liebeskind, L.S. (2000) *Org. Lett.*, **2**, 3229–3231; (b) Liebeskind, L.S. and Srogl, J. (2000) *J. Am. Chem. Soc.*, **122**, 11260–11261.
551 (a) Savarin, C., Srogl, J., and Liebeskind, L.S. (2001) *Org. Lett.*, **3**, 91–93; (b) Liebeskind, L.S. and Srogl, J. (2002) *Org. Lett.*, **4**, 979–981; (c) Kusturin, C.L. and Liebeskind, L.S. (2002) *Org. Lett.*, **4**, 983–985.
552 Kusturin, C., Liebeskind, L.S., Rahman, H., Sample, K., Schweitzer, B., Srogl, J., and Neumann, W.L. (2003) *Org. Lett.*, **5**, 4349–4352.
553 Prokopcova, H. and Kappe, C.O. (2009) *Angew. Chem., Int. Ed.*, **48**, 2276–2286.
554 (a) Ukai, K., Aoki, M., Takaya, J., and Iwasawa, N. (2006) *J. Am. Chem. Soc.*, **128**, 8706–8707; (b) Ohishi, T., Nishiura, M., and Hou, Z.M. (2008) *Angew. Chem., Int. Ed.*, **47**, 5792–5795.
555 Miura, T. and Murakami, M. (2007) *Chem. Commun.*, 217–224.
556 Miura, T., Toyashima, T., and Murakami, M. (2008) *Org. Lett.*, **10**, 4887–4889.
557 Matsuda, T., Makino, M., and Murakami, M. (2004) *Org. Lett.*, **6**, 1257–1259.
558 Tsoi, Y.-T., Zhou, Z., Chan, A.S.C., and Yu, W.-Y. (2010) *Org. Lett.*, **12**, 4506–4509.
559 Ohmiya, H., Yokokawa, N., and Sawamura, M. (2010) *Org. Lett.*, **12**, 438–440.
560 Chu, L. and Qing, F.-L. (2010) *Org. Lett.*, **12**, 5060–5063.
561 McManus, H.A., Fleming, M.J., and Lautens, M. (2007) *Angew. Chem., Int. Ed.*, **46**, 433–436.
562 (a) Zhang, G., Peng, Y., Cui, L., and Zhang, L. (2009) *Angew. Chem., Int. Ed.*, **48**, 3112–3115; (b) Zhang, G., Cui, L., Wang, Y., and Zhang, L. (2010) *J. Am. Chem. Soc.*, **132**, 1474–1475.
563 Patel, S.J. and Jamison, T.F. (2003) *Angew. Chem., Int. Ed.*, **42**, 1364–1367.
564 Huang, T.-H., Chang, H.-M., Wu, M.-Y., and Cheng, C.-H. (2002) *J. Org. Chem.*, **67**, 99–105.
565 Kakiuchi, F., Kan, S., Igi, K., Chatani, N., and Murai, S. (2003) *J. Am. Chem. Soc.*, **125**, 1698–1699.
566 Kakiuchi, F., Usui, M., Ueno, S., Chatani, N., and Murai, S. (2004) *J. Am. Chem. Soc.*, **126**, 2706–2707.
567 (a) Delcamp, J.H., and White, M.C. (2006) *J. Am. Chem. Soc.*, **128**, 15076–15077; (b) Giri, R., Mangel, N., Li, J.-J., Wang, D.-H., Breazzano, S.P., Saunders, L.B., and Yu, J.-Q. (2007) *J. Am. Chem. Soc.*, **129**, 3510–3511; (c) Sun, C.-L., Liu, N., Li, B.-J., Yu, D.-G., Wang, Y., and Shi, Z.-J. (2010) *Org. Lett.*, **12**, 184–187.

568 Chen, X., Goodhue, C.E., and Yu, J.-Q. (2006) *J. Am. Chem. Soc.*, **128**, 12634–12635.

569 Seiple, I.B., Su, S., Rodriguez, R.A., Gianatassio, R., Fujiwara, Y., Sobel, A.L., and Baran, P.S. (2010) *J. Am. Chem. Soc.*, **132**, 13194–13196.

570 Wen, J., Zhang, J., Chen, S.-Y., Li, J., and Yu, X.-Q. (2008) *Angew. Chem., Int. Ed.*, **47**, 8897–8900.

571 Zou, G., Wang, Z., Zhu, J., and Tang, J. (2003) *Chem. Commun.*, 2438–2439.

572 Farrington, E.J., Brown, J.M., Barnard, C.F.J., and Rowsell, E. (2002) *Angew. Chem., Int. Ed.*, **41**, 169–171.

573 Koike, T., Du, X., Sanada, T., Danda, Y., and Mori, A. (2003) *Angew. Chem., Int. Ed.*, **42**, 89–92.

574 (a) Cho, C.S. and Uemura, S. (1994) *J. Organomet. Chem.*, **465**, 85–92; (b) Du, X., Suguro, M., Hirabayashi, K., Mori, A., Nishikata, T., Hagiwara, N., Kawata, K., Okeda, T., Wang, H.F., Fugami, K., and Kosugi, M. (2001) *Org. Lett.*, **3**, 3313–3316; (c) Jung, Y.C., Mishra, R.K., Yoon, C.H., and Jung, K.W. (2003) *Org. Lett.*, **5**, 2231–2234; (d) Lindh, J., Enquist, P.-A., Pilotti, A., Nilsson, P., and Larhead, M. (2007) *J. Org. Chem.*, **72**, 7957–7962; (e) Ruan, J., Li, X., Saidi, O., and Xiao, J. (2008) *J. Am. Chem. Soc.*, **130**, 2424–2425; (f) Delcamp, J.H., Brucks, A.P., and White, M.C. (2008) *J. Am. Chem. Soc.*, **130**, 11270–11271; (g) Su, Y. and Jiao, N. (2009) *Org. Lett.*, **11**, 2980–2983; (h) Werner, E.W. and Sigman, M.S. (2010) *J. Am. Chem. Soc.*, **132**, 13981–13983.

575 Crowley, J.D., Hanni, K.D., Lee, A.-L., and Leigh, D.A. (2007) *J. Am. Chem. Soc.*, **129**, 12092–12093.

576 Xiong, D.-C., Zhang, L.-H., and Xe, X.-S. (2009) *Org. Lett.*, **11**, 1709–1712.

577 Rao, H., Fu, H., Jiang, Y., and Zhao, Y. (2010) *Adv. Synth. Catal.*, **352**, 458–462.

578 Yu, J.-Y., Shimizu, R., and Kuwano, R. (2010) *Angew. Chem., Int. Ed.*, **49**, 6396–6399.

579 Sakai, M., Ueda, M., and Miyaura, N. (1998) *Angew. Chem., Int. Ed.*, **37**, 3279–3281.

580 Sakai, M., Hayashi, H., and Miyaura, N. (1997) *Organometallics*, **16**, 4229–4231.

581 Hayashi, T. and Yamasaki, K. (2003) *Chem. Rev.*, **103**, 2829–2844.

582 Qin, C., Chen, J., Wu, H., Cheng, J., Zhang, Q., Zuo, B., Su, W., and Ding, J. (2008) *Tetrahedron Lett.*, **49**, 1884–1888.

583 Bouffard, J. and Itami, K. (2009) *Org. Lett.*, **11**, 4410–4413.

584 Iwai, Y., Gligorich, K.M., and Sigman, M.S. (2008) *Angew. Chem., Int. Ed.*, **47**, 3219–3222.

585 (a) Oh, C.H., Jung, H.H., Kim, K.S., and Kim, N. (2003) *Angew. Chem., Int. Ed.*, **42**, 805–808; (b) Zou, G., Zhu, J., and Tang, J. (2003) *Tetrahedron Lett.*, **44**, 8709–9711; (c) Gupta, A.K., Kim, K.S., and Oh, C.H. (2005) *Synlett*, 457–460.;

586 (a) Ma, S., Jiao, N., and Ye, L. (2003) *Chem. Eur. J.*, **9**, 6049–6056; (b) Oh, C.H., Ahn, T.W., and Reddy, V.R. (2003) *Chem. Commun.*, 2622–2623.

587 Shirakawa, E., Takahashi, G., Tsuchimoto, T., and Kawakami, Y. (2002) *Chem. Commun.*, 2210–2211.

588 Morikawa, S., Michigami, K., and Amii, H. (2010) *Org. Lett.*, **12**, 2520–2523.

589 Tomita, D., Kanai, M., and Shibasaki, M. (2006) *Chem. Asian J.*, **1**, 161–166.

590 Yamamoto, Y., Kurihara, K., and Miyaura, N. (2009) *Angew. Chem., Int. Ed.*, **48**, 4414–4416.

591 Ueda, M., Saito, A., and Miyaura, N. (2000) *Synlett*, 1637–1639.

592 (a) Kuriyama, M., Soeta, T., Hao, X., Chen, Q., and Tomioka, K. (2004) *J. Am. Chem. Soc.*, **126**, 8128–8129; (b) Beenan, M.A., Weix, D.J., and Ellman, J.A. (2006) *J. Am. Chem. Soc.*, **128**, 6304–6305.

593 Takada, E., Hara, S., and Suzuki, A. (1993) *Tetrahedron Lett.*, **34**, 7067–7070.

594 Chong, J.M., Shen, L., and Taylor, N.J. (2000) *J. Am. Chem. Soc.*, **122**, 1822–1823.

595 (a) Wu, T.R. and Chong, J.M. (2005) *J. Am. Chem. Soc.*, **127**, 3244–3245; (b) Wu, T.R. and Chong, J.M. (2007) *J. Am. Chem. Soc.*, **129**, 3244–3245.

596 Pellegrinet, S.C. and Goodman, J.M. (2006) *J. Am. Chem. Soc.*, **128**, 3116–3117.

597 (a) Lee, S. and MacMillan, D.W.C. (2007) *J. Am. Chem. Soc.*, **129**, 15438–15439; (b) Kim, S.-G. (2008) *Tetrahedron Lett.*, **49**,

6148–6151; (c) Choi, K.-S. and Kim, S.-G. (2010) *Tetrahedron Lett.*, **51**, 5203–5206.
598 Moquist, P.N., Kodama, T., and Schaus, S.E. (2010) *Angew. Chem., Int. Ed.*, **49**, 7096–7100.
599 Blais, J., L'Honoré, A., Soulié, J., and Cadiot, P. (1974) *J. Organomet. Chem.*, **78**, 323–337.
600 (a) Hall, D.G. (2007) *Synlett*, 1644–1655; (b) Lachance, H. and Hall, D.G. (2009) *Organic Reactions*, vol. **73** (ed. S.E. Denmark), John Wiley & Sons, Inc., New York, pp. 1–624.
601 (a) Kennedy, J.W.J. and Hall, D.G. (2002) *J. Am. Chem. Soc.*, **124**, 11586–11587; (b) Ishiyama, T., Ahiko, T.-a., and Miyaura, N. (2002) *J. Am. Chem. Soc.*, **124**, 12414–12415; (c) Rauniyar, V. and Hall, D.G. (2004) *J. Am. Chem. Soc.*, **126**, 4518–4519.
602 Yu, S.H., Ferguson, M.J., McDonald, R., and Hall, D.G. (2005) *J. Am. Chem. Soc.*, **127**, 12808–12809.
603 (a) Rauniyar, V. and Hall, D.G. (2007) *Angew. Chem., Int. Ed.*, **45**, 2426–2428; (b) Rauniyar, V., Zhai, H.M., and Hall, D.G. (2008) *J. Am. Chem. Soc.*, **130**, 8481–8490; (c) Rauniyar, V. and Hall, D.G. (2009) *J. Org. Chem.*, **74**, 4236–4241; (d) Jain, P. and Antilla, J. C. (2010) *J. Am. Chem. Soc.* **132**, 11884–11886.
604 Petasis, N.A. and Akritopoulou, I. (1993) *Tetrahedron Lett.*, **34**, 583–586.
605 (a) Petasis, N.A. and Zavialov, I.A. (1997) *J. Am. Chem. Soc.*, **119**, 445–446; (b) Petasis, N.A. and Zavialov, I.A. (1998) *J. Am. Chem. Soc.*, **120**, 11798–11799.
606 Lou, S. and Schaus, S.E. (2008) *J. Am. Chem. Soc.*, **130**, 6922–6923.
607 Candeias, N.R., Montalbano, F., Cal, P.M.S.D., and Gois, P.M.P. (2010) *Chem. Rev.*, **110**, 6169–6193.
608 Chan, D.M.T., Monaco, K.L., Wang, R.-P., and Winters, M.P. (1998) *Tetrahedron Lett.*, **39**, 2933–2936.
609 Evans, D.A., Katz, J.L., and West, T.R. (1998) *Tetrahedron Lett.*, **39**, 2937–2940.
610 Lam, P.Y.S., Clark, C.G., Saubern, S., Adams, J., Winters, M.P., Chan, D.M.T., and Combs, A. (1998) *Tetrahedron Lett.*, **39**, 2941–2944.
611 (a) Combs, A.P., Saubern, S., Rafalski, M., and Lam, P.Y.S. (1999) *Tetrahedron Lett.*, **40**, 1623–1626; (b) Combs, A.P., Tadesse, S., Rafalski, M., Haque, T.S., and Lam, P.Y.S. (2002) *J. Comb. Chem.*, **4**, 179–182.
612 Morgan, J. and Pinhey, J.T. (1990) *J. Chem. Soc., Perkin Trans.* **1**, 715–722.
613 (a) Peng, C., Wang, Y., and Wang, J. (2008) *J. Am. Chem. Soc.*, **130**, 1566–1567; (b) Peng, C., Zhang, W., Yan, G., and Wang, J. (2009) *Org. Lett.*, **11**, 1667–30.
614 Barluenga, J., Tomás-Gamasa, M., Aznar, F., and Valdés, C. (2009) *Nat. Chem.*, **1**, 494–499.
615 Mizojiri, R. and Kobayashi, Y. (1995) *J. Chem. Soc., Perkin Trans. 1*, 2073–2075.
616 Trost, B.M. and Spagnol, M.D. (1995) *J. Chem. Soc., Perkin Trans.* **1**, 2083–2096.
617 Retbϕll, M., Edwards, A.J., Rae, A.D., Willis, A.C., Bennett, M.A., and Wenger, E. (2002) *J. Am. Chem. Soc.*, **124**, 8348–8360.
618 Minutolo, F. and Katzenellenbogen, J.A. (1998) *J. Am. Chem. Soc.*, **120**, 13264–13625.
619 Melhado, A.D., Brenzovich, W.E., Jr., Lackner, A.D., and Toste, F.D. (2010) *J. Am. Chem. Soc.*, **132**, 8885–8887.
620 Wang, W., Jasinski, J., Hammond, G.B., and Xu, B. (2010) *Angew. Chem., Int. Ed.*, **49**, 7247–7252.
621 Nakamura, M., Hatakeyama, T., Hara, K., Fukudome, H., and Nakamura, E. (2004) *J. Am. Chem. Soc.* **126**, 14344–14345.
622 Fandrick, D.R., Reeves, J.T., Tan, Z., Lee, H., Song, J.J., Yee, N.K., and Senanayake, C.H. (2009) *Org. Lett.*, **11**, 5458–5461.
623 Dickschat, A. and Studer, A. (2010) *Org. Lett.*, **12**, 3972–3974.
624 Hayakawa, H., Okada, N., and Miyashita, M. (1999) *Tetrahedron Lett.*, **40**, 3191–3194.
625 Hirai, A., Yu, X.-Q., Tonooka, T., and Miyashita, M. (2003) *Chem. Commun.*, 2482–2483.
626 Falck, J.R., Bondlela, M., Venkataraman, S.K., and Srinivas, D. (2001) *J. Org. Chem.*, **66**, 7148–7150.
627 Körner, C., Starkov, F., and Sheppard, T.D. (2010) *J. Am. Chem. Soc.*, **132**, 5968–5969.

628 Li, D.R., Murugan, A., and Falck, J.R. (2008) *J. Am. Chem. Soc.*, **130**, 46–48.

629 (a) Ishihara, K. and Yamamoto, H. (1999) *Eur. J. Org. Chem.*, 527–538; (b) Georgiou, I., Ilyashenko, G., and Whiting, A. (2009) *Acc. Chem. Res.*, **42**, 756–768.

630 (a) Letsinger, R.L., Dandegaonker, S., Vullo, W.J., and Morrison, J.D. (1963) *J. Am. Chem. Soc.*, **85**, 2223–2227; (b) Letsinger, R.L. and Morrison, J.D. (1963) *J. Am. Chem. Soc.*, **85**, 2227–2229.

631 Letsinger, R.L. and MacLean, D.B. (1963) *J. Am. Chem. Soc.*, **85**, 2230–2236.

632 Ishihara, K., Ohara, S., and Yamamoto, H. (1996) *J. Org. Chem.*, **61**, 4196–4197.

633 Al-Zoubi, R.M., Marion, O., and Hall, D.G. (2008) *Angew. Chem., Int. Ed.*, **47**, 2876–2879.

634 Aelvoet, K., Batsanov, A.S., Blatch, A.J., Grosjean, C., Patrick, L.G.F., Smethurst, C.A., and Whiting, A. (2008) *Angew. Chem., Int. Ed.*, **47**, 768–770.

635 (a) Zheng, H. and Hall, D.G. (2010) *Chem. Eur. J.*, **16**, 5454–5460; (b) Zheng, H. and Hall, D.G. (2010) *Tetrahedron Lett.*, **51**, 3561–3564.

636 McCubbin, J.A., Hosseini, H., and Krokhin, O.V. (2010) *J. Org. Chem.*, **75**, 959–962.

637 Zheng, H., Lejkowski, M., and Hall, D.G. (2011) *Chemical Science*, **2**, 1305–1310.

638 Rao, G. and Philipp, M. (1991) *J. Org. Chem.*, **56**, 505–512.

639 Barker, S.A., Hatt, B.W., and Somers, P.J. (1973) *Carbohydr. Res.*, **26**, 41–53.

640 Rohovec, J., Kotek, J., Peters, J.A., and Maschmeyer, T. (2001) *Eur. J. Org. Chem.*, 3899–3901.

641 de Vries, J.G. and Hubbard, S.A. (1988) *J. Chem. Soc., Chem. Commun.*, 1172–1173.

642 Narasaka, K., Shimada, G., Osoda, K., and Iwasawa, N. (1991) *Synthesis*, 1171–1172.

643 Nicolaou, K.C., Liu, J.J., Yang, Z., Ueno, H., Sorensen, E.J., Claiborne, C.F., Guy, R.K., Hwang, C.-K., Nakada, M., and Nantermet, P.G. (1995) *J. Am. Chem. Soc.*, **117**, 634–644.

644 (a) Nagata, W., Okada, K., and Aoki, T. (1979) *Synthesis*, 365–368; (b) Murphy, W.S., Tuladhar, S.M., and Duffy, B. (1992) *J. Chem. Soc., Perkin Trans.* **1**, 605–609; (c) Pettigrew, J.D., Cadieux, J.A., So, S.S.S., and Wilson, P.D. (2005) *Org. Lett.*, **7**, 467–470; (d) Zheng, H. and Hall, D.G. (2010) *Tetrahedron Lett.*, **51**, 4256–4259.

645 (a) Molander, G.A., Bobbitt, K.L., and Murry, C.K. (1992) *J. Am. Chem. Soc.*, **114**, 2759–2760; (b) Molander, G.A. and Bobbitt, K.L. (1993) *J. Am. Chem. Soc.*, **115**, 7517–7518.

646 Sailes, H.E., Watts, J.P., and Whiting, A. (2000) *J. Chem. Soc., Perkin Trans. 1*, 3362–3374.

647 Charette, A.B., Juteau, H., Lebel, H., and Molinaro, C. (1998) *J. Am. Chem. Soc.*, **120**, 11943–11952.

648 (a) Ferrier, R.J., Prasad, D., and Rudowski, A. (1965) *J. Chem. Soc.*, 858–863; (b) Ferrier, R.J. (1978) *Adv. Carbohydr. Chem. Biochem.*, **35**, 31–80.

649 (a) Dahlhoff, W.V. and Köster, R. (1982) *Heterocycles*, **18**, 421–449; (b) Dahlhoff, W.V., Fenzl, W., and Köster, R. (1990) *Liebigs Ann. Chem.*, 807–810.

650 Dahlhoff, W.V. and Köster, R. (1980) *Synthesis*, **1980**, 936–937.

651 Langston, S., Bernet, B., and Vasella, A. (1994) *Helv. Chim. Acta*, **77**, 2341–2353.

652 (a) Oshima, K., Kitazono, E.-i., and Aoyama, Y. (1997) *Tetrahedron Lett.*, **38**, 5001–5004; (b) Oshima, K. and Aoyama, Y. (1999) *J. Am. Chem. Soc.*, **121**, 2315–2316; (c) Kaji, E., Nishino, T., Ishige, K., Ohya, Y., and Shirai, Y. (2010) *Tetrahedron Lett.*, **51**, 1570–1573.

653 Yurkevich, A.M., Kolodkina, I.I., Varshavskaya, L.S., Borodulina-Shvetz, V.I., Rudakova, I.P., and Preobrazhenski, N.A. (1969) *Tetrahedron*, **25**, 477–484.

654 McMurry, J.E. and Erion, M.D. (1985) *J. Am. Chem. Soc.*, **107**, 2712–2720.

655 Perun, T.J., Martin, J.R., and Egan, R.S. (1974) *J. Org. Chem.*, **39**, 1490–1493.

656 Liljebris, C., Nilsson, B.M., Resul, B., and Hacksell, U. (1996) *J. Org. Chem.*, **61**, 4028–4034.

657 Flores-Parra, A., Paredes-Tepox, C., Joseph-Nathan, P., and Contreras, R. (1990) *Tetrahedron*, **46**, 4137–4148.

658 Bertounesque, E., Florent, J.-C., and Monneret, C. (1991) *Synthesis*, 270–272.

659 Hungerford, N.L., McKinney, A.R., Stenhouse, A.M., and McLeod, M.D. (2006) *Org. Biomol. Chem.*, **4**, 3951–3959.

660 (a) Ishihara, K., Kuroki, Y., Hanaki, N., Ohara, S., and Yamamoto, H. (1996) *J. Am. Chem. Soc.*, **118**, 1569–1570; (b) Kuroki, Y., Ishihara, K., Hanaki, N., Ohara, S., and Yamamoto, H. (1998) *Bull. Chem. Soc. Jpn.*, **71**, 1221–1230.

661 (a) Evans, D.A. and Polniaszek, R.P. (1986) *Tetrahedron Lett.*, **27**, 5683–5686; (b) Evans, D.A., Polniaszek, R.P., DeVries, K.M., Guinn, D.E., and Mathre, D.J. (1991) *J. Am. Chem. Soc.*, **113**, 7613–7630.

662 Kaupp, G., Naimi-Jamal, M.R., and Stepanenko, V. (2003) *Chem. Eur. J.*, **9**, 4156–4160.

663 Iwasawa, N., Kato, T., and Narasaka, K. (1988) *Chem. Lett.*, 1721–1724.

664 (a) Gypser, A., Michel, D., Nirschl, D.S., and Sharpless, K.B. (1998) *J. Org. Chem.*, **63**, 7322–7327; (b) Hovelmann, C. H. and Muniz, K. (2005) *Chem. Eur. J.* **11**, 3951–3958.

665 Barker, S.A., Hatt, B.W., Somers, P.J., and Woodbury, R.R. (1973) *Carbohydr. Res.*, **26**, 55–64.

666 (a) Seymour, E. and Fréchet, J.M.J. (1976) *Tetrahedron Lett.*, **15**, 1149–1152; (b) Farrall, M.J. and Fréchet, J.M.J. (1976) *J. Org. Chem.*, **41**, 3877–3882.

667 Bullen, N.P., Hodge, P., and Thorpe, F.G. (1981) *J. Chem. Soc., Perkin 1*, 1863–1867.

668 (a) Weith, H.L., Wiebers, J.L., and Gilham, P.T. (1970) *Biochemistry*, **9**, 4396–4401; (b) Rosenberg, M., Wiebers, J.L., and Gilham, P.T. (1972) *Biochemistry*, **11**, 3623–3628.

669 (a) Schott, H. (1972) *Angew. Chem., Int. Ed. Engl.*, **11**, 824–825; (b) Schott, H., Rudloff, E., Schmidt, P., Roychoudhury, R., and Kössel, H. (1973) *Biochemistry*, **12**, 932–938.

670 Johnson, B.J.B. (1981) *Biochemistry*, **20**, 6103–6108.

671 (a) Zhang, L., Xu, Y., Yao, H., Xie, L., Yao, J., Lu, H., Yang, P., Dou, P., Liang, L., He, J., Liu, Z., and Chen, H.-Y. (2009) *J. Chromatogr. A*, **1216**, 7558–7563; (b) Frasconi, M., Tel-Vered, R., Riskin, M., and Willner, I. (2010) *Anal. Chem.*, **82**, 2512–2519.

672 (a) Li, X., Pennington, J., Stobaugh, J.F., and Schöneich, C. (2008) *Anal. Biochem.*, **372**, 227–236; (b) Xu, Y., Wu, Z., Zhang, L., Lu, H., Yang, P., Webley, P.A., and Zhao, D. (2009) *Anal. Chem.*, **81**, 503–508.

673 (a) Mazzeo, J.R. and Krull, I.S. (1989) *Biochromatography*, **4**, 124–130; (b) Singhal, R.P. and DeSilva, S.S.M. (1992) *Adv. Chromatogr.*, **31**, 293–335; (c) Liu, X.-C. and Scouten, W.H. (2005) Chapter 8, in *Handbook of Affinity Chromatography*, 2nd edn (ed. D.S. Hage), CRC Press, pp. 215–226;(d) Liu, X.-C. (2006) *Chin. J. Chromatogr.*, **24**, 73–80.

674 Nishiyabu, R., Kubo, Y., James, T.D., and Fossey, J.S. (2010) *Chem. Commun.*, 1106–1123.

675 (a) Mallia, A.K., Hermanson, G.T., Krohn, R.I., Fujimoto, E.K., and Smith, P.K. (1981) *Anal. Lett.*, **14** (B8), 649–661; (b) Middle, F.A., Bannister, A., Bellingham, A.J., and Dean, P.D.G. (1983) *Biochem. J.*, **209**, 771–779; (c) Zhang, Q., Schepmoes, A.A., Brock, J.W.C., Wu, S., Moore, R.J., Purvine, S.O., Baynes, J.W., Smith, R.D., and Metz, T.O. (2008) *Anal. Chem.*, **80**, 9822–9829.

676 Miyazaki, H., Kikuchi, A., Koyama, Y., Okano, T., Sakurai, Y., and Kataoka, K. (1993) *Biochem. Biophys. Res. Commun.*, **195**, 829–836.

677 Kataoka, K., Miyazaki, H., Okano, T., and Sakurai, Y. (1994) *Macromolecules*, **27**, 1061–1062.

678 Kikuchi, A., Suzuki, K., Okabayashi, O., Hoshino, H., Kataoka, K., Sakurai, Y., and Okano, T. (1996) *Anal. Chem.*, **68**, 823–828.

679 Gabai, R., Sallacan, N., Chegel, V., Bourenko, T., Katz, E., and Willner, I. (2001) *J. Phys. Chem. B*, **105**, 8196–8202.

680 Kanekiyo, Y., Sano, M., Iguchi, R., and Shinkai, S. (2000) *J. Pol. Sci. A*, **38**, 1302–1310.

681 Seymour, E. and Fréchet, J.M.J. (1976) *Tetrahedron Lett.*, **17**, 3669–3672.

682 Ren, L., Liu, Z., Liu, Y., Dou, P., and Chen, H.-Y. (2009) *Angew. Chem., Int. Ed.*, **48**, 6704–6707.

683 Glad, M., Norrlöw, O., Sellergren, B., Siegbahn, N., and Mosbach, K. (1985) *J. Chromatogr.*, **347**, 11–23.

684 Wulff, G. and Schauhoff, S. (1991) *J. Org. Chem.*, **56**, 395–400.

685 Fréchet, J.M.J., Nuyens, L.J., and Seymour, E. (1979) *J. Am. Chem. Soc.*, **101**, 432–436.

686 (a) Belogi, G., Zhu, T., and Boons, G.-J. (2000) *Tetrahedron Lett.*, **41**, 6965–6968; (b) Belogi, G., Zhu, T., and Boons, G.-J. (2000) *Tetrahedron Lett.*, **41**, 6969–6972.

687 Hsiao, H.-Y., Chen, M.-L., Wu, H.-T., Huang, L.D., Chien, W.-T., Yu, C.-C., Jan, F.-D., Sahabuddin, S., Chang, T.-C., and Lin, C.-C. (2010) *Chem. Commun.*, **47**, 1187–1189.

688 Chen, M.L., Adak, A.K., Yeh, N.C., Yang, W.B., Chuang, Y.J., Wong, C.H., Hwang, K.C., Hwu, J.R.R., Hsieh, S.L., and Lin, C.C. (2008) *Angew. Chem., Int. Ed.*, **47**, 8627–8630.

689 Polsky, R., Harper, J.C., Wheeler, D.R., Arango, D.C., and Brozik, S.M. (2008) *Angew. Chem., Int. Ed.*, **47**, 2631–2634.

690 (a) James, T.D., Sandanayake, K.R.A.S., and Shinkai, S. (1996) *Angew. Chem., Int. Ed.*, **35**, 1910–1922; (b) James, T.D. and Shinkai, S. (2002) *Topp. Curr. Chem.*, **218**, 159–200; (c) Wang, W., Gao, X., and Wang, B. (2002) *Curr. Org. Chem.*, **6**, 1285–1317; (d) Cao, H.S. and Heagy, M.D. (2004) *J. Fluoresc.*, **14**, 569–584; (e) Yan, J., Fang, H., and Wang, B.H. (2005) *Med. Res. Rev.*, **25**, 490–520; (f) James, T.D. (2007) *Top. Curr. Chem.*, **277**, 107–152;
(g) Galbraith, E. and James, T.D. (2010) *Chem. Commun.*, **39**, 3831–3842;
(h) Jin, S., Cheng, Y.F., Reid, S., Li, M.Y., and Wang, B.H. (2010) *Med. Res. Rev.*, **30**, 171–257.

691 Schiller, A., Wessling, R.A., and Singaram, B. (2007) *Angew. Chem., Int. Ed.*, **46**, 6457–6459.

692 Pal, A., Bérubé, M., and Hall, D.G. (2010) *Angew. Chem., Int. Ed.*, **49**, 1492–1495.

693 Li, M., Liu, N., Huang, Z., Du, L., Altier, C., Fang, H., and Wang, B. (2008) *J. Am. Chem. Soc.*, **130**, 12636–12638.

694 (a) Zhao, J., Fyles, T.M., and James, T.D. (2004) *Angew. Chem., Int. Ed.*, **43**, 3461–3464; (b) Levonis, S.M., Kiefel, M.J., and Houston, T.A. (2009) *Chem. Commun.*, 2278–2280; (c) Matsumoto, A., Sato, N., Kataoka, K., and Miyahara, Y. (2009) *J. Am. Chem. Soc.*, **131**, 12022–12023.

695 (a) Coskun, A. and Akkaya, E.U. (2004) *Org. Lett.*, **6**, 3107–3109; (b) Secor, K.E. and Glass, T.E. (2004) *Org. Lett.*, **6**, 3727–3730.

696 Maue, M. and Schrader, T. (2005) *Angew. Chem., Int. Ed.*, **44**, 2265–2270.

697 Hagihara, S., Tanaka, H., and Matile, S. (2008) *J. Am. Chem. Soc.*, **130**, 5656–5657.

698 (a) Gray, C.W., Jr., and Houston, T.A. (2002) *J. Org. Chem.*, **67**, 5426–5428; (b) Houston, T.A., Levonis, S.M., and Kiefel, M.J. (2007) *Aust. J. Chem.*, **60**, 811–815.

699 (a) Lavigne, J.J. and Anslyn, E.V. (1999) *Angew. Chem., Int. Ed.*, **38**, 3666–3669; (b) Nguyen, B.T., Wiskur, S.L., and Anslyn, E.V. (2004) *Org. Lett.*, **6**, 2499–2501.

700 (a) Groziak, M. (2001) *Am. J. Ther.*, **8**, 321–328; (b) Yang, W., Gao, X., and Wang, B. (2003) *Med. Res. Rev.*, **23**, 346–368;(c) Yang, W., Gao, X., and Wang, B.H. (2005) Chapter 13, in *Boronic Acids*, 1st edn (ed. D.G. Hall), Wiley-VCH Verlag GmbH, Weinheim.

701 (a) Vogels, C.M., Nikolcheva, L.G., Spinney, H.A., Norman, D.W., Baerlocher, M.O., Baerlocher, F.J., and Westcott, S.A. (2001) *Can. J. Chem.*, **79**, 1115–1123; (b) King, A.S., Nikolcheva, L.G., Graves, C.R., Kaminski, A., Vogels, C.M., Hudson, R.H.E., Ireland, R.J., Duffy, S.J., and Westcott, S.A. (2002) *Can. J. Chem.*, **80**, 1217–1222; (c) Irving, A.M., Vogels, C.M., Nikolcheva, L.G., Edwards, J.P., He, X.-F., Hamilton, M.G., Baerlocher, M.O., Baerlocher, F.J., Decken, A., and Westcott, S.A. (2003) *New J. Chem.*, **27**, 1419–1424; (d) Jabbour, A., Steinberg, D., Dembitsky, V.M., Moussaieff, A., Zaks, B., and Srebnik, M. (2004) *J. Med. Chem*, **47**, 2409–2410.

702 (a) Gronowitz, S., Dalgren, T., Namtvedt, J., Roos, C., Sjöberg, B., and Forsgren, U. (1971) *Acta Pharm. Suec.*, **8**,

377–390; (b) Högenauer, G. and Woisetschläger, M. (1981) *Nature*, **293**, 662–664.
703 Baldock, C., de Boer, G.-J., Rafferty, J.B., Stuitje, A.R., and Rice, D.W. (1998) *Biochem. Pharmacol.*, **55**, 1541–1549.
704 Baldock, C., Rafferty, J.B., Sedelnikova, S.E., Baker, P.J., Stuitje, A.R., Slabas, A.R., Hawkes, T.R., and Rice, D.W. (1996) *Science*, **274**, 2107–2110.
705 Robinson, P.D. and Groziak, M.P. (1999) *Acta. Crystallogr.*, **C55**, 1701–1704.
706 Feng, Z. and Hellberg, M. (2000) *Tetrahedron Lett.*, **41**, 5813–5814.
707 Tondi, D., Calo, S., Shoichet, B.K., and Costi, M.P. (2010) *Bioorg. Med. Chem. Lett.*, **20**, 3416–3419.
708 Suzuki, N., Suzuki, T., Ota, Y., Nakano, T., Kurihara, M., Okuda, H., Yamori, T., Tsumoto, H., Nakagawa, H., and Miyata, N. (2009) *J. Med. Chem.*, **52**, 2909–2922.
709 Nakamura, H., Kuroda, H., Saito, H., Suzuki, R., Yamori, T., Maruyama, K., and Haga, T. (2006) *ChemMedChem*, **1**, 729–740.
710 Inglis, S.R., Zervosen, A., Woon, E.C.Y., Gerards, T., Teller, N., Fischer, D.S., Luxen, A., and Schofield, C.J. (2009) *J. Med. Chem.*, **52**, 6097–6106.
711 Rock, F.L. *et al.* (2007) *Science*, **316**, 1759–1761.
712 (a) Akama, T., Baker, S.J., Zhang, Y.K., Hernandez, V., Zhou, H.C., Sanders, V., Freund, Y., Kimura, R., Maples, K.R., and Plattner, J.J. (2009) *Bioorg. Med. Chem. Lett.*, **19**, 2129–2132; (b) Ding, D.Z. *et al.* (2010) *ACS Med. Chem. Lett.*, **1**, 165–169.
713 Jay, J.I., Lai, B.E., Myszka, D.G., Mahalingam, A., Laugheinrich, K., Katz, D.F., and Kiser, P.F. (2010) *Mol. Pharm.*, **7**, 116–129.
714 (a) Akparov, V.K. and Stepanov, V.M. (1978) *J. Chromatogr.*, **155**, 329–336; (b) Cartwright, S. and Waley, S. (1984) *Biochem. J.*, **221**, 505–512.
715 Tsilikounas, E., Kettner, C.A., and Bachovkin, W.W. (1992) *Biochemistry*, **31**, 12839–12846.
716 Tsilikounas, E., Kettner, C.A., and Bachovkin, W.W. (1993) *Biochemistry*, **32**, 12651–12655.
717 Stoll, V.S., Eger, B.T., Hynes, R.C., Martichonok, V., Jones, J.B., and Pai, E.F. (1998) *Biochemistry*, **37**, 451–462.
718 Adams, J.A. (1998) *Bioorg. Med. Chem. Lett.*, **8**, 333–338.
719 Paramore, A. and Frantz, S. (2003) *Nat. Rev. Drug Discov.*, **2**, 611–612.
720 (a) Soloway, A.H., Tjarks, W., Barnum, B.A., Rong, F.-G., Barth, R.F., Codogni, I.M., and Wilson, J.G. (1998) *Chem. Rev.*, **98**, 1515–1562; (b) Barth, R.F., Coderre, J.A., Vicente, M.G.H., and Blue, T.E. (2005) *Clin. Cancer Res.*, **11**, 3987–4002; (c) Yamamoto, T., Nakai, K., and Matsumura, A. (2008) *Cancer Lett.*, **262**, 143–152; (d) Barth, R.F. (2009) *Appl. Radiat. Isot.*, **67**, S3–S6.
721 Kankaanranta, L., Seppala, T., Koivunoro, H., Saarilahti, K., Atula, T., Collan, J., Salli, E., Kortesniemi, M., Uusi-Simola, J., Makitle, A., Seppanen, M., Minn, H., Kotiluoto, P., Auterinen, I., Savolainen, S., Kouri, M., and Joensuu, H. (2007) *Int. J. Radiat. Oncol. Biol. Phys.*, **69**, 475–482.
722 Yanagie, H., Ogata, A., Sugiyama, H. *et al.* (2008) *Expert Opin. Drug Deliv.*, **5**, 427–443.
723 Shinbo, T., Nishimura, K., Yamaguchi, T., and Sugiura, M. (1986) *J. Chem. Soc., Chem. Commun.*, 349–351.
724 Mohler, L.K. and Czarnik, A.W. (1993) *J. Am. Chem. Soc.*, **115**, 2998–2999.
725 Reetz, M.T., Huff, J., Rudolph, J., Töllner, K., Deege, A., and Goddard, R. (1994) *J. Am. Chem. Soc.*, **116**, 11588–11589.
726 Paugam, M.-F., Bien, J.T., Smith, B.D., Chrisstoffels, L.A.J., de Jong, F., and Reinhoudt, D.N. (1996) *J. Am. Chem. Soc.*, **118**, 9820–9825.
727 Duggan, P.J. (2004) *Aust. J. Chem.*, **57**, 291–299.
728 Smith, B.D. and Gardiner, S.J. (1999) *Advances in Supramolecular Chemistry*, vol. **5** (ed. G.W. Gokel), JAI Press, pp. 157–202.
729 Duggan, P.J., Houston, T.A., Kiefel, M.J., Levonis, S.M., Smith, B.D., and Szydzik, M.L. (2008) *Tetrahedron*, **64**, 7122–7126.
730 Kashiwada, A., Tsuboi, M., and Matsuda, K. (2009) *Chem. Commun.*, 695–697.

731 Frantzen, F., Grimsrud, K., Heggli, D.-E., and Sundrehagen, E. (1995) *J. Chromatogr. B*, **670**, 37–45.

732 Wiley, J.P., Hughes, K.A., Kaiser, R.J., Kesicki, E.A., Lund, K.P., and Stolowitz, M.L. (2001) *Bioconjug. Chem.*, **12**, 240–250.

733 Halo, T.L., Appelbaum, J., Hobert, E.H., Balkin, D.M., and Schepartz, A. (2009) *J. Am. Chem. Soc.*, **131**, 438–439.

734 Chalker, J.M., Wood, C.S., and Davis, B.G. (2009) *J. Am. Chem. Soc.*, **131**, 16346–16347.

735 DeSantis, G., Paech, C., and Jones, J.B. (2000) *Bioorg. Med. Chem.*, **8**, 563–570.

736 Frantzen, F., Grimsrud, K., Heggli, D.-E., and Sundrehagen, E. (1997) *Clin. Chim. Acta*, **263**, 207–224.

737 Burnett, T.J., Peebles, H.C., and Hageman, J.H. (1980) *Biochem. Biophys. Res. Commun.*, **96**, 157–162.

738 Vandenburg, Y.R., Zhang, Z.-Y., Fishkind, D.J., and Smith, B.D. (2000) *Chem. Commun.*, 149–150.

739 (a) Yang, W., Gao, S., Gao, X., Karnati, V.V.R., Ni, W., Wang, B., Hooks, W.B., Carson, J., and Weston, B. (2002) *Bioorg. Med. Chem. Lett.*, **12**, 2175–2177; (b) Yang, W., Fan, H., Gao, X., Gao, S., Karnati, V.V.R., Ni, W., Hooks, W.B., Carson, J., Weston, B., and Wang, W. (2004) *Chem. Biol.*, **11**, 439–448.

740 Miller, E.W., Albers, A.E., Pralle, A., Isacoff, E.Y., and Chang, C.J. (2005) *J. Am. Chem. Soc.*, **127**, 16652–16659.

741 Dickinson, B.C., Huynh, C., and Chang, C.J. (2010) *J. Am. Chem. Soc.*, **132**, 5906–5915.

742 Gao, C., Lavey, B.J., Lo, C.-H.L., Datta, A., Wenworth, P., Jr., and Janda, K.D. (1998) *J. Am. Chem. Soc.*, **120**, 2212–2217.

743 (a) Brustad, E., Bushey, M.L., Lee, J.W., Groff, D., Liu, W., and Schultz, P.G. (2008) *Angew. Chem., Int. Ed.*, **47**, 8220–8223; (b) Liu, C.C., Mack, A.V., Brustad, E.M., Mills, J.H., Groff, D., Smider, V.V., and Schultz, P.G. (2009) *J. Am. Chem. Soc.*, **131**, 9616–9617.

744 Hoeg-Jensen, T., Havelund, S., Nielsen, P.K., and Markussen, J. (2005) *J. Am. Chem. Soc.*, **127**, 6158–6159.

745 Fujita, N., Shinkai, S., and James, T.D. (2008) *Chem. Asian J.*, **3**, 1076–1091.

746 Nishiyabu, R., Kubo, Y., James, T.D., and Fossey, J.S. (2010) *Chem. Commun.*, 1124–1150.

747 (a) Liu, W., Pink, M., and Lee, D. (2009) *J. Am. Chem. Soc.*, **131**, 8703–8707; (b) Liu, W., Huang, W., Pink, M., and Lee, D. (2010) *J. Am. Chem. Soc.*, **132**, 11844–11846.

748 Korich, A.L., Clarke, K.M., Wallace, D., and Iovine, P.M. (2009) *Macromolecules*, **42**, 5906–5908.